# ACUTE RESPIRATORY FAILURE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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# INTRODUCTION

In 1852, A.M.D. Guilbert published a book titled *The Art of Healing and Preventing Diseases* (1) that contains some interesting observations:

> Dans la maladie chronique, la cause est la, les organes sont altérés par son long séjour; on peut toujours chasser la cause à volonté, mais les organes ne se répareront que s'ils sont encore réparables.

And further along in the text:

> Les poumons étant peu sensibles en général, leurs maladies peuvent être irrévocablement mortelles, longtemps avant la mort.

In many ways, these statements constitute an apt description of the natural history of chronic obstructive pulmonary disease (COPD).

During the two decades following World War II, considerable attention was given to the condition we now call COPD. Back in those days, COPD was alternatively called chronic bronchitis or emphysema. Later, with the advent of blood gas measurements, the patients were labeled "pink puffers" or "blue bloaters" depending on their physiological manifestations.

And then, little by little, pulmonary medicine became an established subspecialty and basic and clinical research on the lung in health and disease became

a fruitful and successful endeavor. As many other lung diseases were recognized and some causes were discovered, interest in COPD waned. After all, it was accepted that lung tissue is not reparable and that its death is irrevocable, leading inexorably to the death of the patient.

Yet, COPD remains an enormous public health problem in both the western world and developing countries. In the United States alone, 10 to 12 million people suffer from COPD, and the adjusted death rate from this disease continues to increase while it steadily decreases for other diseases. Because of enormous advances in the understanding of the pathophysiology of COPD, patients now survive longer; however, over time, they experience unavoidable acute respiratory failure, an event often superimposed on a chronic dysfunction. It is fortunate that we can heal and even perhaps prevent these acute events, at least in the early phase of the disease.

At the same time, as Moran Campbell implies in his foreword, COPD may have become a forgotten disease because of its lack of glamour and its eventual hopelessness.

This book is intended to redress the situation. It brings together all that we know about acute respiratory failure in COPD patients. Let us be candid about it: we do not know a lot, and perhaps fail to use all we do know. And all of it in this volume makes this volume, as Dr. Campbell points out, a unique resource.

The editors, Drs. Derenne and Similowski from France and Dr. Whitelaw from Canada, have assembled a roster of international contributors whose expertise is recognized worldwide. For this reason, this volume represents the best schools of thought about a clinical problem of great significance. It should aid clinical practitioners and investigators as well. I am most appreciative to the editors and authors for giving the Lung Biology in Health and Disease series the opportunity to include this important contribution.

**Claude Lenfant, M.D.**
Bethesda, Maryland

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# FOREWORD

During the late 1940s and early 1950s, I was a house officer at a hospital in central London. Each winter we had an influx of patients whose disorders today would be described by the title of this book. However, the terms in this title did not yet exist, and the patients were variously labeled as having bronchitis-in-relapse, bronchopneumonia, cor pulmonale, or emphysema. We really didn't know what we were dealing with. Blood gases could not be measured and the broad concepts of respiratory physiology were not publicly known. It is true that the three-compartment model and its relatives were in the literature, but they had not been grasped by most clinicians. I had read the papers of Riley and others, but in the absence of methods for measuring blood gases the concepts were really inapplicable.

Our treatment of these patients reflected our ignorance. There was an understandable emphasis on antibiotic therapy. Digitalis and diuretics were freely prescribed. Most patients didn't receive any oxygen. Some authorities supported this practice because they felt that the administration of oxygen would interfere with adaptive mechanisms. Other authorities used very high concentrations of oxygen. Some used intermittent oxygen. In London, during the early 1950s, thanks largely to Westlake, there was a widespread recognition of the danger of $CO_2$ narcosis.

At autopsy, the findings in the lungs of such patients were predictable: areas of collapse, swollen bronchi, mucopurulent sputum, patches of pneumonia, and a variable amount of emphysema. Perhaps most symptomatic of our lack of understanding was the fact that the term *respiratory failure* itself was used not in the way it is today but rather to describe any patient incapacitated by breathlessness.

I had the great good fortune to spend most of 1955 at Johns Hopkins with Richard Riley. From him I learned the notorious bubble method, and from him and the others in the lab I gained a grasp of his views of gas exchange.

I returned to London and for the next five or six years, as each winter's crop of patients came in, Westlake, Howell, McNicol, and I nibbled at various aspects of the problem—the role of stimulants, indirect (rebreathing) methods of measuring $PCO_2$, the state of the patients on arrival at the hospital, and, particularly, controlled oxygen therapy. The climate of opinion at that time was that these patients required tracheostomy and that it should be performed promptly, before they had deteriorated. My original idea was that controlled oxygen therapy would identify those patients who required such prompt tracheostomy. The conclusion that controlled oxygen could obviate the need for tracheostomy and similar heroic measures gradually dawned on me and was based solely on anecdotal experience.

Since the early 1960s, my involvement with this form of respiratory failure has become indirect. I have not been in the front line but I continue to see numbers of these patients "after the event" and watch the literature. Without wishing to abuse the privilege of writing this foreword, I would like to say that I am unhappy that *low flow* oxygen has come to be interpreted as synonymous with *controlled* oxygen. I think the aim of oxygen therapy should be to increase the delivery of oxygen rather than to reach any arbitrary concentration in the arterial blood.

More generally, I would support those centers that "know their patients" so that relapses of respiratory failure can be promptly and conservatively managed.

Considering how common acute on chronic respiratory failure is, there have been few systematic studies on the subject. Perhaps this is not surprising: because COPD is not a "glamorous" problem, respiratory failure in COPD is usually handled by junior medical staff (in early stages, even by nonmedical staff); and those who publish papers are usually sequestered in intensive care units and such places where the state of patients is by no means unadulterated.

These last points I have made perhaps to some extent explain why this book is the first major work devoted to the problem. I welcome it and wish it well.

**E. J. Moran Campbell**
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# PREFACE

We are very pleased to present this book in the Lung Biology in Health and Disease series. Two previous volumes, edited by Dr. Thomas L. Petty, in 1978 and 1985, gave summaries of knowledge about clinical and pathological aspects of chronic obstructive pulmonary disease (COPD) in general. In this volume, we have focused attention on the episodes of acute respiratory failure that threaten the lives of COPD patients and bring them to hospitals and intensive care units. Our aim has been to provide a detailed and up-to-date analysis of the corresponding problems and clinical management.

In the past 15 years, there have been several major changes in the way we think about COPD and respiratory failure. One is the recognition that respiratory failure is to a large extent a problem of the respiratory muscles. A new body of knowledge about the muscles and their predicament in severe COPD has sprung up. The possible significance of muscle fatigue in acute failure remains an important topic for discussion in research. Second is the recognition that expiratory flow limitation plays a decisive role in severe COPD and that the intrinsic positive end-expiratory pressure (PEEP) that accompanies hyperinflation is a major load to inspiratory muscles. Recent investigations into control of breathing and dyspnea in COPD and acute failure make this topic increasingly complex and show that the traditional simple hypothesis of impaired $CO_2$ sensitivity to explain

$CO_2$ retention when oxygen is given is only partly correct. The search for causes and the way to prevent episodes of acute failure is driving new work in the area of bronchial infection, while advances in understanding of hemodynamics and heart–lung interaction promise to provide new approaches to supportive treatment.

The advent of various means of noninvasive ventilatory support is another recent breakthrough in the management of acute respiratory failure of COPD. Spectacular results reported with continuous positive airway pressure (CPAP), inspiratory pressure support, or assist–control ventilation delivered via nasal or face masks have now blurred the traditional distinction between conservative treatment and mechanical ventilation by invasive means. They have already begun to change the attitude of clinicians faced with an aging and increasingly fragile population of patients, and will probably, in the near future, lead to new approaches in decision-making and estimate of prognosis.

It is certainly timely to assemble this new knowledge in all of these areas in one volume, and we have been fortunate to have the support of so many expert contributors from institutions in both Europe and North America. They represent a truly international spirit of research and practice in this field. We are grateful to them for the amount of time and work they have devoted to this book.

Many of us have drawn inspiration for studies in this area from the ideas of Dr. E. J. Moran Campbell, who pioneered in thinking about respiratory muscles and control of breathing in lung diseases, and we are truly indebted to him for providing the foreword to this book.

We are also grateful to Dr. Lenfant for his encouragement, and to the staff at Marcel Dekker, Inc., for overcoming the difficulties of actual publication.

We hope this book will help prompt a new generation of clinicians and scientists to pursue the search for better understanding of the process of acute respiratory failure and better approaches to management.

**Jean-Philippe Derenne**
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# CONTENTS

# 1

# Introduction

## Definition and Clinical Presentation

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### I. Definition

This volume presents various aspects of the clinical entity known as acute respiratory failure of chronic obstructive pulmonary disease (COPD). Patients with COPD have frequent episodes during which they feel worse than usual and function poorly in their daily life. The worst of these episodes bring them to hospital with dyspnea or confusion and require acute management. Acute respiratory failure (ARF) is narrowly defined as a situation where there is evidence of acute failure of the ventilatory pump shown by a rise in arterial $P_{CO_2}$ above its chronic stable level or deterioration in arterial oxygen to potentially dangerous levels. Many patients dealt with in emergency rooms do not satisfy arbitrary definitions needed for the purpose of epidemiology but do have acute disturbances of function of the same kind but of lesser degree, and obviously require similar clinical analysis and treatment in order to forestall development of full-blown acute respiratory failure.

## II. Clinical Assessment

The history and physical examination determine whether more involved and expensive evaluations of biochemical and physiological variables or radiographic imaging should be done. In emergency situations, history and physical examination guide all of the initial treatment decisions. The usefulness of these clinical tools is not easy to evaluate but is worth considering carefully.

### A. History

The history and physical examination are used to estimate a pretest probability of any diagnosis and thus determine the accuracy of the conclusion from any test that is done (1). The history serves to alert the clinician to particular causes of acute deterioration and to the presence of other diseases that may complicate the purely respiratory problem (heart disease, endocrine disturbance, neuromuscular disease, renal failure, diabetes, and so on). The history of previous episodes of ARF and previous data about special features of COPD in the particular patient are obviously important, especially response to bronchodilators and steroids, and use of drugs that may effect acid-base status, respiratory center activity, bronchomotor tone, respiratory muscle strength, and cardiovascular status. In practice, distress and confusion of the patient often limit the extent and accuracy of the clinical history. The ability of specific historical points such as chest pain, cough, sputum, hemoptysis, and fever to discriminate the various common precipitating causes of ARF has not been examined except in the example of pulmonary embolism, where they seem to be rather unhelpful (2). When it is available, the complete record of the patient's previous assessments and the details of any previous episodes of acute respiratory failure often contain the most useful information.

### B. Physical Examination

The accuracy of diagnosis through physical signs has been studied to some extent in patients with chronic stable COPD. There are important problems of interobserver variation and of sensitivity and specificity of individual physical signs (3–13). Indrawing or retraction of the soft tissues in the suprasternal and supraclavicular during inspiration correlates with a degree of obstruction in stable COPD patients (7), but Stubbing et al. (10) found that this worked well for only one of their two observers and was strongly influenced by the age of the patient. They also found that the more signs of obstruction were observed in one patient, the lower his $FEV_1$ was likely to be.

#### *Forced Expiratory Time*

Forced expiratory time can be used as a clinical substitute for measuring $FEV_1$ (7,14,15) and can be useful for clinical detection of COPD, but is not applicable for evaluating patients with ARF.

### *Tracheal Descent*

Tracheal descent, evaluated by placing a finger on the thyroid curtilage, correlates with amplitude of pleural pressure swings (16). It is not specific for COPD, but in COPD the degree of descent correlates with degree of obstruction (7,10).

### *General Appearance*

The general aspect of the patient is difficult to categorize but is one of the most important features. In addition to the assembly of specific physical signs that allow an experienced clinician to recognize severe COPD, a general impression of distress or fatigue is often strong enough to impel a decision to intubate and begin mechanical ventilation. Attempts to specify a formula or a particular criterion for this decision, such as pulse rate, respiratory rate, cyanosis, or degree of confusion, are not likely to be convincing. COPD patients often sit upright or lean forward and support themselves on their arms to fix the muscles of the shoulder and neck. This posture is thus not useful for diagnosis of left heart failure in these patients. On the other hand, the supine posture has also been shown to be comfortable and to increase the effectiveness of the diaphragm in some COPD patients (17).

### *Appearance and Movement of the Chest Wall*

The barrel-shaped chest with increased anteroposterior (AP) diameter is part of the classic description of COPD but is hard to categorize with any specificity. Kyphosis, often found in older people, produces a chest with an increased AP diameter and is often associated with COPD. AP diameter, or the ratio of AP to lateral diameter, is never measured and the assessment depends on a visual impression. Correlation between respiratory function and estimates of chest shape in stable COPD patients is weak.

Abnormal movements of the lower part of the rib cage in inspiration can be plausibly explained by mechanical principles related to hyperinflation. Normally, the lower part of the rib cage is subject to an inward force vector due to negative pleural pressure in inspiration and an outward force vector due to positive abdominal pressure applied in the region where the diaphragm lies along the inside of the rib cage (the area of apposition) as well as the direct muscle tension vectors of the diaphragm and the abdominal muscle wall. (The usual analysis neglects any effect of abdominal muscle wall tension, which has not been measured). With the diaphragm in its usual position in normal subjects, diaphragm tension runs upward and is tangential to the inner surface of the rib cage. There is a large area of apposition. The outward force, equal to abdominal pressure multiplied by the area of apposition, exceeds the inward force, equal to pleural pressure ($P$pl) multiplied by the area over which $P$pl is applied to the inside of the lower part of rib cage. The lower part of the rib cage therefore moves outward. When the diaphragm descends, the area of apposition decreases, and the area over which the negative

pleural pressure is applied increases. When the diaphragm descends to the point where there is no longer an area of apposition, the tension of the diaphragm stops being tangential along the inside of the ribs and has a inward radial component, which adds to the tendency of the ribs to move inward. In the most commonly discussed sign of Hoover (10,18), the lower part of the lateral rib cage moves inward in inspiration. A more subtle abnormality can be detected anteriorly where the rib margins ascend toward the lower end of the sternum. In some patients who do not have the standard Hoover sign, inward movement in inspiration of the rib cage near the tips of the seventh and eighth ribs can be detected by palpation with the finger tips of each hand lightly applied to a point on the upward curving margin of the anterior rib cage (Fig. 1). A similar movement can be seen in many normal subjects as they inspire close to total lung capacity (R.A.L. Brewis, unpublished observations).

The chest should be examined for symmetry of movement, which may be the clue to a large pneumothorax, pneumonia, pleurisy, or an obstructed airway, although asymmetry might be expected to be less sensitive in COPD patients than in normal patients because the excursion of their chest wall for a given change in volume is less.

Paradoxical movements of the rib cage and abdomen have been described in COPD in ARF (19,20) but are rare in stable COPD (21). (See Fig. 2.) These movements are best appreciated by palpation, with one hand resting tightly on the sternum and one on the abdomen near the umbilicus. They are associated with worse prognosis (20). Cohen et al. (21a) have described "respiratory alternans" in which patients switch back and forth from emphasizing expansion of the rib cage for a series of breaths to emphasizing expansion of the abdomen. They associated this with evidence of respiratory muscle fatigue. The analogy has been made of a person carrying a heavy suitcase who switches it back and forth from one hand to the other.

### *Use of Accessory Muscles*

Normal people contract their scalene muscles during quiet inspiration but this can usually not be detected clinically, only by electromyography. Clinically detectable contraction of the scalenes was described by Magendie (22), who termed it the "respiratory pulse." There is some ongoing confusion in the literature and in textbooks about activity of the sternocleidomastoids, beginning from the time of Beau and Massiat (23), who used "respiratory pulse" to indicate contraction of these muscles and claimed that they, not the scalenes, were active in asthma patients. A recent electromyographic study found no evidence for activity of sternocleidomastoid muscles in stable COPD patients (24).

Most of the confusion can be avoided if clinicians recognize that visual observation is completely unreliable for judging activity of the neck accessory

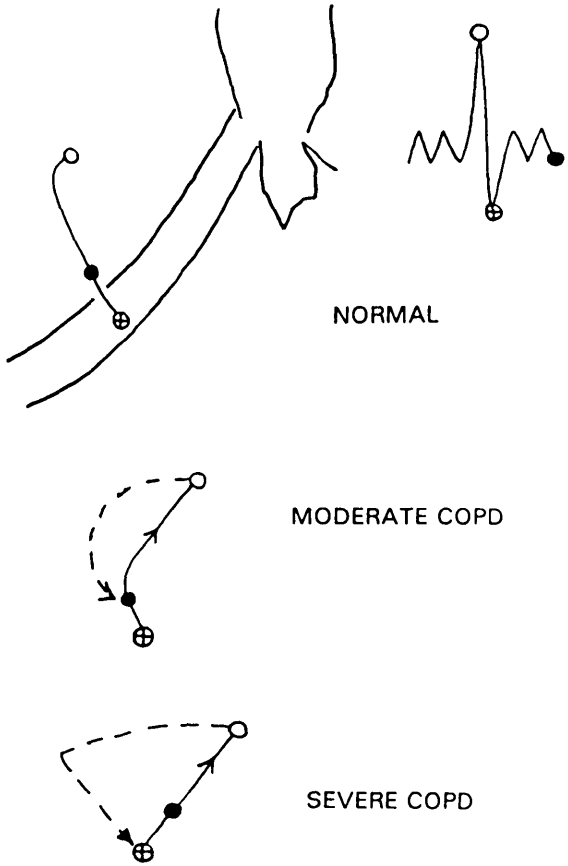


**Figure 1** Motion of the anterior margin of the rib cage during breathing. The motion can best be appreciated by placing the fingertips of each hand on the costal margins about 10 cm below the xiphoid process. Solid circle, position at FRC; open circle, TLC; crossed circle, RV. Solid line, locus of the point during active inspiration. Dashed line, passive expiration. (From R. A. L. Brewis, unpublished.)

muscles. The scalenes are invisible in all but the thinnest, most wasted patients. On the other hand, inspiratory retraction of soft tissues at the base of the neck can make the outlines of the bodies of scalene and sternocleidomastoid muscles stand out, giving a false appearance of activity. The only reliable clinical method is by palpation. Contraction of the scalenes is sought by the tips of fingers aimed horizontally from an anterolateral aspect at the floor of the posterior triangle of the neck, of the sternocleidomastoids by grasping the body of the muscle lightly

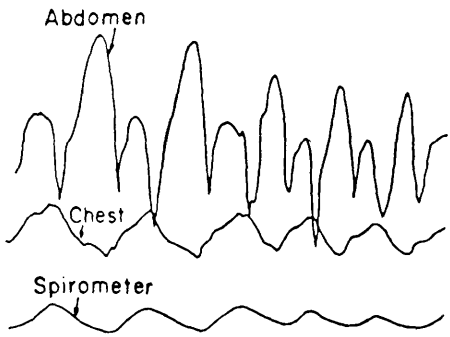


**Figure 2** Abnormal motion of rib cage and abdomen in patients with severe COPD in ARF. (From Ref. 19.)

between thumb and forefinger. The muscles can clearly be felt to tense at the end of inspiration if they are moderately active, or throughout inspiration if they are strongly activated. Patients with ARF of COPD do use their scalenes and usually their sternocleidomastoids; in some thin patients the fibers of the trapezius that run over the upper edge of the bulk of this muscle and insert on the clavicle can be seen to contract. These clinical signs of very high respiratory motor output correspond to the high occlusion pressures seen in ARF of COPD. The authors have also observed inspiratory protrusion of the tongue in a few obese patients with ARF of COPD. In these cases the high motor activity of genioglossus muscles peculiar to patients with high upper airway resistance and sleep apnea syndrome (25) may be added to the high general inspiratory motor output of ARF of COPD. Associated with contraction of neck muscles is a greater than normal upward movement of the clavicle, which is seen in severe COPD (26) and in acute severe asthma (27).

### *Cyanosis and Hypercapnia*

The accuracy of clinical detection of cyanosis for estimation of actual $Po_2$ is debatable (28–31). During emergency room encounters with COPD patients, the ideal lighting and the precise observations by a clinician practiced in detection of cyanosis are not usually available. Objective studies of clinical cyanosis have focused on the level of unsaturated hemoglobin required to give just detectable cyanosis. In COPD in acute failure, the percentage of unsaturated hemoglobin is often well above that threshold, but the ability of clinicians to evaluate different grades of cyanosis and use that to estimate more severe degrees of desaturation has not been studied.

It is accepted that the symptoms and physical signs associated with hypercapnia (headache, bounding pulse, papilledema, and asterixis) are very insensi-

tive. It is a maxim that direct measurement of arterial blood gases is indispensable for any assessment of ventilatory or acid-base status that is to be used in making clinical decisions.

#### *Respiratory Rate*

Respiratory rate may be one of the most useful signs for evaluating COPD patients in the emergency room. Studies of pattern of breathing in stable COPD patients show that respiratory rate goes up and tidal volume goes down as the disease progresses (32). Patients with severe COPD not in ARF have rates of about 23/min. By comparison, patients admitted to critical care with ARF of COPD have a rate of about 32/min on average, and this declines over the first few days of successful treatment toward the rates found in stable patients (33).

#### *Pursed Lips Breathing*

Pursed lips breathing is used by some, but not all, COPD patients. Those who do use it do so more when in distress, such as on exercise, or in ARF.

## III. Diagnosis of the Precipitating Cause

The commonly considered causes for acute worsening of ventilatory status in patients with COPD are bronchial infection, bronchospasm, left ventricular failure, pneumonia, pneumothorax, and thromboembolism. Other contributing possibilities are sleep apnea, use of sedatives or narcotics, aspiration, and metabolic alkalosis. Against a background of severe COPD, most of these diagnoses are difficult to prove or to exclude, so treatment is often necessarily speculative.

### A. Bacterial Infection

Bronchial bacterial infections are suspected when there is a history of increasing volume or purulent appearance of the sputum, especially if associated with other symptoms of upper respiratory infection. The reliability of bacteriological tests on the sputum is poor, and treatment trials using antibacterials with a spectrum against usual respiratory pathogens, while shown to be helpful on an average in some trials, may also predispose to more serious nosocomial infections in some cases. (See Chapter 12).

Criteria for diagnosis of pneumonia are arbitrary and are even more doubtful for patients in critical care with multisystem disease than in patients who are less ill. Some combination of fever, sputum, white blood cell count, and chest X-ray change is usually required. In COPD, however, the chest X-ray is less sensitive than usual for detecting pulmonary infiltrates.

### B. Viral and Mycoplasmal Infection

There have been many investigations examining the role of viruses and of *Mycoplasma pneumoniae* in acute exacerbations of COPD, and the results are controversial (34–39). Parainfluenza viruses have been the ones most commonly associated with the acute illness (36,37,39). However Gump et al. (36) also identified rhinoviruses, influenza viruses, and coronaviruses in their study, and Smith et al. (38) reported that influenza viruses were associated with the most severe cases. Together, all respiratory viruses and *M. pneumoniae* have been identified in 12–63% of the patients undergoing an acute exacerbation of COPD (36,37), but these organisms can also be found in many patients in a stable condition. It has been reported that smoking, particularly in COPD patients, is associated with an increased susceptibility to viral infections of the airways, but this is still under scrutiny (40–43). The seasonal incidence of viral infections is well known, and a thorough epidemiological study conducted in Harris County, Texas, found that the peak occurrence of hospitalization in the study hospitals coincided with the peak of influenza virus activity in the years 1978–1981 (44). Hospitalization in subjects older than 65 years of age was most commonly associated with chronic pulmonary disorders, in most cases with COPD (45,46).

If careful studies using the modern techniques of virology should prove that viruses play an important role in the acute deterioration of COPD patients, important therapeutic prospects, both preventive and curative, would appear.

### C. Bronchospasm

Bronchospasm or bronchial edema from asthma or bronchial inflammation due to nonspecific hyperactivity is difficult to prove or exclude because of the variance in measurements of bronchial patency, such as $FEV_1$ and airways resistance. A change of 20–40% in FEV, which would certainly imply a substantial change in mechanical load on the system, may be only 0.20 L in absolute terms, hard to measure with confidence in a stable patient and even more so in a dyspneic patient in ARF.

### D. Heart Failure

Left ventricular failure is also difficult to exclude or to diagnose with certainty. Elevation of jugular venous pressure and a third heart sound can be found in cor pulmonale, and crackles are a common feature of COPD alone. The chest X-ray in emphysema is less than normally sensitive for detecting interstitial or alveolar edema; the distribution of blood flow judged by caliber of veins is difficult because of preexisting pulmonary hypertension and distortion of vessels by bullae; and enlargement of the cardiac silhouette is hard to assess in emphysema. Echocardiography is often unsuccessful because of overinflated lungs. Interpretation of

hemodynamic measurements is made more difficult by the large respiratory swings in intrathoracic pressure. In addition, there is reason to expect that pulmonary function may deteriorate much more for a given rise in pulmonary capillary wedge pressure in COPD than in normal subjects (47), because small increases in interstitial fluid, which produce small changes in airway diameter, will cause much larger increases in resistance of the narrow airways of COPD than of normal airways. Impairment in left ventricular function that is near or below the threshold of detection by current methods may therefore be capable of aggravating respiratory failure in COPD.

### E. Pulmonary Thromboembolism

As discussed in Chapter 14, similar considerations apply to thromboembolism. The presence of COPD makes methods for detecting emboli less precise, while at the same time there is reason to expect that smaller emboli, hard to detect even in subjects with previously normal lungs, could have more important effects in COPD than in other patients.

### F. Pneumothorax

Pneumothorax can be difficult to detect in COPD and in patients in intensive care and demands a high index of suspicion and sometimes use of CT scanning for diagnosis.

### G. Strategies

Physicians reply to all of the uncertainties about diagnosis with a wide range of strategies, and there is always concern about either overtreatment or undertreatment in populations of patients, and even more in individual cases. We need more and better ways to classify and analyze these problems, more reliable and sensitive measurements, and more outcome trials to show the advantages and disadvantages of different approaches to treatment.

It may be helpful to abandon the logic of trying to classify cases into "pneumonia" versus "not pneumonia" or "thromboembolism" versus "not-thromboembolism" or "heart failure" versus "not heart failure" and instead to view infection as a whole continuum in the relationship between host and microorganism from peaceful coexistence to fatal invasion, and clinical thromboembolism as one extreme of an imbalance in the normal continuous process of formation, embolization, filtering, and dissolution of thrombi, and cardiac dysfunction as a graded abnormality whose significance lies in some quantifiable influence it has on pulmonary function rather than whether it reaches an arbitrary threshold of classification as abnormal by an X-ray or wedge pressure criterion. There is an argument here to focus research on finding more precise ways to monitor respira-

tory function in the intensive care unit, to assess whether a pathological process such as infection or cardiac dysfunction is in fact having an important impact on respiration in the individual patient. Perhaps we may also be moving toward an era where biochemical markers of the activity of processes such as thromboembolism and infection can be assayed and used to decide whether it is important to give drugs to reduce formation of thrombi, or to suppress a microorganism whose presence has been detected, or to modify host response to infection.

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# 2

# The Lung Pathology of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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## I. Introduction

Surprisingly little data are available concerning the pathological features of acute exacerbations of chronic obstructive pulmonary disease (COPD). This is mainly because the lungs from these patients only become available when the exacerbations prove fatal. The majority of these studies have been designed to describe and quantify the abnormalities associated with the irreversible component of COPD rather than the acute changes leading to the terminal event. To our knowledge there are no systematic descriptions of the changes associated with terminal events in COPD, and in this chapter we briefly review the established anatomical features of COPD and speculate on how a variety of events might interact with the existing pathology to produce a deterioration in lung function and a worsening of symptoms.

## II. Lung Pathology in COPD

Excellent reviews of the pathology of the lung in COPD are available (1–3). The most important pathological changes that occur in the lung in COPD are those that result in narrowing of peripheral airways and loss of lung elastic recoil.

In early studies of the site of airway narrowing in the lungs of patients who died of COPD, the investigators used high-frequency oscillation to measure total airway resistance and partitioned it into the airway resistance central to and peripheral to airways 2–3 mm in diameter (4). These studies showed that in COPD there was little increase in the resistance of the central airways but there was a marked increase in peripheral airway resistance. Although there subsequently has been controversy over the contribution of the peripheral airways to the total airways resistance in normal lungs, all studies have shown that these airways are the major site of resistance in COPD. Since the increase in peripheral airway resistance could not be reversed by increasing lung volume or transpulmonary pressure, these investigators suggested that the increased resistance was due to structural changes in the peripheral airways rather than the loss of parenchymal support for these airways.

Investigators have subsequently attempted to identify the pathological changes in the peripheral airways that cause the increase in resistance, but none has identified any distinct pathological abnormality that satisfactorily explains the increase in resistance. While inflammation and repair in the small airways are undoubtedly responsible for the abnormalities of function, it is unclear what component or components of the inflammatory and repair processes are critical. Niewoehner et al. (5) showed that inflammation of membranous and respiratory bronchioles is an early pathological lesion in all smokers, but since only 15–20% of smokers develop COPD (6), these lesions do not provide an adequate explanation for the increase in resistance in COPD patients. The lesions seen in established COPD are much less severe than the obvious inflammation and scarring associated with similar degrees of airway obstruction in patients who have bronchiolitis caused by viral infection, toxic gas inhalation, graft-versus-host disease, or connective tissue diseases (7). Cosio et al. (8) and Wright et al. (9) devised semi-quantitative grading schemes to assess the type and magnitude of the various pathological abnormalities that contribute to the airway pathology in the membranous and respiratory bronchioles. These abnormalities include (1) occlusion of the lumen by mucus and cells, (2) mucosal ulceration, (3) goblet cell hyperplasia, (4) squamous cell metaplasia, (5) inflammatory infiltration of the airway wall, (6) increased fibrous tissue in the airway wall, (7) increased muscle in the airway wall, and (8) increased pigment deposition in the airway wall. By assigning a score between 0 and 3 for each of these variables in each airway and by summing these for all airways, they developed a small airway disease score. A number of studies (10–12) have shown that the semi-quantitative changes correlate with the degree of airway narrowing in COPD; in particular, the scores for inflammatory cell infiltration and fibrosis are most closely related to airflow obstruction. However, the structure-function studies show that only a small part of the variability of airway obstruction can be explained by semi-quantitative grading schemes.

Bosken et al. (12) reasoned that airway wall thickening, scarring, and

narrowing would be the final result of chronic inflammation, and they set out to quantify these changes taking advantage of a robust marker of airway size, the basement membrane perimeter ($P_{bm}$), to compare the peripheral airways of smokers with and without significant airflow obstruction. Although they showed significant reductions in luminal diameter and increases in airway wall thickness in obstructed smokers, the magnitude of these differences was small when compared to the large increases in wall thickness seen in patients with stable or fatal asthma (13). The discrepancy between the measurements of peripheral airway resistance and the structural alterations in these airways suggest that functional changes, which are not readily apparent on histological examination, contribute to the airway narrowing and increased resistance. These functional changes could include in vivo smooth muscle contraction, lack of elastic support, and/or an increase in airway liquid surface tension.

The other major pathological change in the lungs of patients with COPD is emphysema. Emphysema is characterized by the destruction of alveolar walls and the coalescence of peripheral airspaces into large holes, which reduce the cross-sectional area of the lung microvasculature and the alveolar surface area available for gas exchange. In smokers, emphysema is located primarily in the center of the lobule (centrilobular or centriacinar emphysema) but can extend to involve the whole lobule (panlobular or panacinar emphysema). The extent and type of emphysema can be estimated using grading schemes for whole lung sections (14) or by measuring the lung surface area using quantitative histology (15). More recently, computed tomography (CT) has been successfully employed to determine the extent of emphysema (16). The link between the structural abnormalities of emphysema and the increased airway resistance and reduced maximal expiratory flow that characterize COPD is through changes in lung elastic recoil. Decreased lung recoil causes airflow obstruction by decreasing the driving force for expiratory flow and by decreasing the support for intraparenchymal airways. If the alveolar wall destruction is diffuse, these two changes—decreased recoil and decreased tethering—should be related. However, if there is preferential loss of alveolar walls in the peribronchial region, as has been suggested by Linhartova et al. (17), there could be disproportionate airway narrowing for a given loss of overall lung recoil. This scenario might explain the failure of lung inflation to correct the increase in peripheral airway resistance (4). However, studies using morphological technique as well as high-resolution CT have shown that emphysematous lung destruction is not invariably associated with airway obstruction and decreased lung elastic recoil pressure (1,18). The lack of a tight correlation between lung recoil and airflow obstruction on the one hand and morphological or radiographic emphysema on the other can be explained by the fact that the pressure-volume characteristics of the lung are primarily determined by the mean alveolar size of the airspaces that participate in lung inflation and deflation. Fully developed centrilobular emphysematous spaces contribute little to the lung pres-

sure volume curve because they remain inflated throughout a vital capacity maneuver (19). Osborne et al. (20) showed that patients may have loss of lung elastic recoil without significant emphysema and similarly there may be substantial emphysema without significant loss of lung elastic recoil. Expiratory obstruction is worse in patients who have both significant emphysema and loss of lung recoil.

Additional pathological changes that occur in the lungs of patients with COPD are summarized in Table 1. These include an increased volume of mucous glands in central airways and dysplastic and metaplastic changes in the airway epithelium. These changes result in a loss of normal ciliated epithelium that combines with increased mucus production to impair mucocillary clearance. The excess mucus that accumulates in the airways may contribute to the increased airflow obstruction and to the severity of lower respiratory tract viral and bacterial infection. The loss of pulmonary capillary bed and alveolar surface area available for diffusion of gases contributes to arterial hypoxemia and hypercapnia. The increased pulmonary vascular resistance caused by destruction of the of capillary bed combines with hypoxic vasoconstriction to produce pulmonary hypertension, which results in remodeling of the vessels, right ventricular hypertrophy, and right ventricular failure.

Let us now consider the precipitating causes of exacerbations of COPD and speculate how the pathological changes associated with these conditions could interact with the existing pathology of COPD to produce deterioration of lung function. The two predominant pathophysiological processes in COPD, airway narrowing and loss of lung recoil, combine to cause expiratory airflow obstruction

**Table 1** Pathological Abnormalities in Chronic Obstructive Pulmonary Disease

| |
|---|
| Airways |
| Mucous gland hyperplasia and hypertrophy |
| Goblet cell hyperplasia |
| Squamous cell metaplasia |
| Inflammation and repair of respiratory and membranous bronchioles |
| Epithelial sloughing |
| Mucus plugging |
| Parenchyma |
| Interstitial and airspace inflammation |
| Centrilobular and panlobular emphysema |
| Loss of alveolar attachments to intraparenchymal airways |
| Bullae |
| Loss of pulmonary capillaries |
| Intimal and medial thickening of pulmonary arteries |

and hyperinflation of the lung. It is the hyperinflation that is primarily responsible for the symptom of breathlessness in COPD, since it increases the elastic work of breathing and places the inspiratory muscles at a severe mechanical disadvantage. Expiratory obstruction exacerbates this problem by causing dynamic hyperinflation during periods of increased respiratory drive, and, in addition, hyperinflation prevents the contribution of expiratory muscle recruitment to inspiration (21). It follows that the pathological changes that result in the development of acute exacerbations of COPD will be processes that increase airflow obstruction or decrease lung recoil. Since exacerbations are largely reversible, and since the major cause of loss of lung recoil is destruction of lung parenchyma, it is unlikely that acute changes in recoil are very important during exacerbations of COPD. On the other hand, an acute "uncoupling" of recoil to intraparenchymal airways as a result of peribronchial inflammation and edema could decrease the support for intraparenchymal airways and have important functional consequences. This reasoning suggests that the pathological processes most likely to exacerbate COPD are those that narrow the lumen of the peripheral airways, whether directly or by reducing the parenchymal support.

The specific conditions likely to have the greatest effect are viral and/or bacterial infections of the lower respiratory tract and lung congestion and edema. These common precipitating factors can cause worsening of expiratory airflow obstruction, increased hyperinflation, gas trapping, and reduced gas exchange. Viral infections are discussed in detail in Chapter 11 and bacterial infections are discussed in Chapter 12.

Viruses characteristically invade respiratory epithelial cells, cause the cells to lyse, and provoke a local inflammatory response in an attempt to clear the virus from the respiratory tract (22). They also cause a systemic response that includes fever and leukocytosis and results in increased metabolic demand for oxygen. The inflammation of the airway epithelium further increases respiratory mucus production from glands and goblet cells and inhibits the already deficient mucocillary clearance mechanisms. The resultant mucosal edema as well as the intraluminal accumulation of mucus and cellular debris can contribute to airway narrowing. The exudate associated with the inflammatory response in the airways generates inflammatory mediators from the complement, coagulation, and kinin systems and increases the surface tension of the fluid that lines the peripheral airways. These changes tend to narrow the airways by causing the airway smooth muscle to contract and by replacing the surfactant in the peripheral airways with a liquid of much higher surface tension.

Some viral proteins can themselves have a detrimental effect on airway function. For instance, neuraminidase, which is produced by influenza virus, is known to cleave sialic acid from cell membranes and may enhance the cellular inflammatory response (23). Neuraminidase also lowers the viscosity of the mucous film in the respiratory tract, encouraging the spread of virus and conceiv-

ably having a detrimental effect on the viscoelastic properties of the mucus, resulting in decreased clearance. The damage to respiratory epithelial cells exposes sensory nerve endings, and irritation of these endings causes local release of tachykinins, such as substance P, which can increase the inflammatory response and enhance cholinergic reflex–induced airway narrowing (24). In addition to an increase in the release of inflammatory peptides, damage to the respiratory epithelium leads to a loss of the enzyme neutral endopeptidase, which normally metabolizes tachykinins (25). Thus, viral inflammation causes both an increase in production of inflammatory tachykinins and a reduction in their metabolism.

It is well known that even normal subjects develop prolonged alterations in airway responsiveness to nonspecific stimuli following viral infections. Experimental upper respiratory tract infection in normal volunteers can cause subsequent airway hyperresponsiveness (26). These changes in lung function and airway responsiveness can persist for up to 6 weeks after a viral infection. It is likely that in patients who have COPD and established airway inflammation and hyperresponsiveness, the same virus-induced changes will have an enhanced effect in causing exacerbation of airflow obstruction and a worsening of nonspecific responsiveness. The potential consequences of latent or persistent viral infections as amplifiers of the chronic inflammatory response are further discussed in Chapter 11.

Bacterial infections are also a cause of exacerbations of COPD. One mechanism by which airflow obstruction is worsened in bacterial infection is through the action of endotoxin. Inhalation of live *Haemophilus influenzae* organisms causes biphasic bronchial obstruction in patients with COPD, an effect that can be mimicked with endotoxin (27). Normal subjects exposed to endotoxin develop an acute decrease in lung function, and it has been shown that bacterial endotoxin is responsible for the respiratory symptoms in humidifier disease and the decrease in lung function associated with chronic exposure to cotton dust in byssinosis (28).

The second major contributor to exacerbations of COPD is pulmonary and bronchovascular congestion and edema. Although the edema that accumulates during exacerbations of COPD is generally attributed to right heart failure, coexistent left heart dysfunction and generalized fluid retention can increase pulmonary and bronchial microvascular pressure leading to edema of the airway wall, especially if the simultaneous presence of inflammation increases microvascular permeability. The functional consequences of even slight accumulations of excess interstitial fluid in the airway wall may be considerable. Figure 1 shows a schematic of an intraparenchymal airway. The airway wall can be divided into three functionally distinct layers: the inner airway wall from the inner border of the airway smooth muscle to the luminal surface, the smooth muscle layer, and the adventitial layer between the outer border of the smooth muscle and the surrounding parenchyma. Edema accumulation in any of these compartments can exacerbate airway narrowing simply by encroaching on the airway lumen. The accumulation

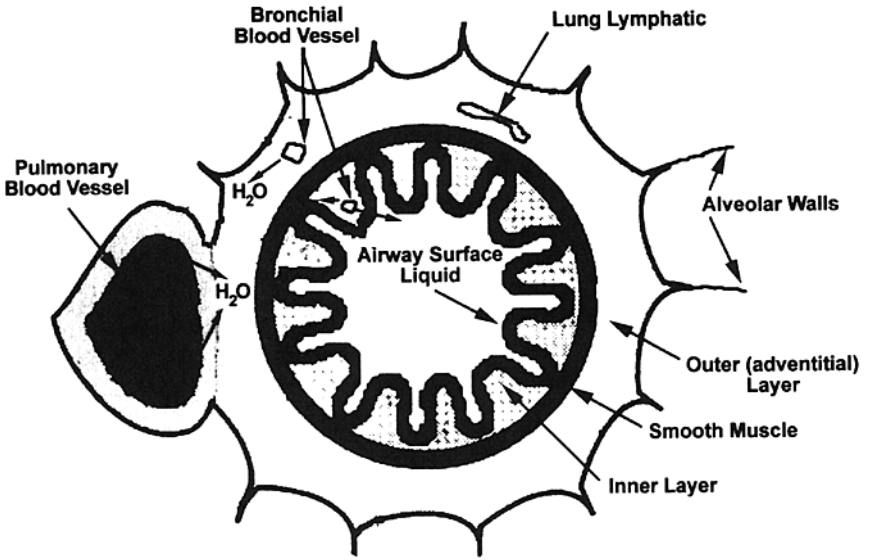


**Figure 1** This schematic representation of an intraparenchymal airway shows the three layers: the inner wall area between the smooth muscle and the lumen, the smooth muscle area, and the outer or adventitial wall area between the smooth muscle and the surrounding parenchyma. Fluid from the pulmonary vessels, the bronchial vessels, and lung lymphatics can accumulate in the wall as well as in the lumen during exacerbations of COPD.

of excess fluid in the outer (adventitial) or inner (submucosal) compartments has additional functional consequences, which may be extremely important in exacerbations of COPD. Edema of the inner wall compartment can cause an exaggeration in the airway narrowing produced by any amount of airway smooth muscle shortening. The potential importance of this mechanism can be appreciated using some simple calculations. Thickening of the inner airway walls sufficient to double baseline resistance can increase by 10 times the magnitude of the airway narrowing produced by moderate airway smooth muscle contraction and shortening.

An accumulation of fluid in the adventitial compartment between the outer border of the smooth muscle and the surrounding parenchyma may have similar important consequences in COPD. It is through this adventitial compartment that the tethering force of the lung parenchyma is transmitted to the airway wall. Thickening of the adventitial compartment will functionally uncouple lung recoil from airway recoil. The combination of decreased recoil and an accumulation of fluid in the adventitial compartment may have disastrous consequences for lung function during exacerbations of COPD. When these changes combine to narrow

peripheral airways, the only method to compensate is to breathe at higher lung volume. The hyperinflation puts the respiratory muscles at a mechanical disadvantage, resulting in the need for increased neural drive, which causes worsening breathlessness. The encroachment of residual volume causes an increase in elastic load, and these factors combine to cause tachypnea, which worsens the dynamic hyperinflation and the "auto-PEEP" that develops behind the flow-limited small airways.

Patients with cor pulmonale secondary to COPD have increased lung extravascular water (29). Increased systemic venous pressure combined with fluid overload increase lung water and cause abnormalities of airway function in experimental animals (30). There are two reasons why the adventitial airway compartment may be the site of excessive fluid accumulation during exacerbations of COPD. First, the bronchial microvessels drain, in part, to the right heart. The increased systemic venous pressure that accompanies right heart dysfunction in COPD will produce increases in bronchial microvascular pressure, thereby encouraging airway edema. If there is coexistent left heart failure and generalized fluid retention, the capillary pressure in the bronchial microvessels that anastomose with the pulmonary circulation will also be increased. The second cause for interstitial accumulation of fluid around airways is the anatomical arrangement by which lymph drains from the lung via the right lymphatic duct and thoracic duct into the systemic venous system at the junctions of the subclavian and jugular veins. Right heart failure that develops during exacerbations of COPD reduces the drainage of the lung interstitium by the pulmonary lymphatics and results in bronchial and peribronchial edema. These changes reduce airway function by thickening the airway wall, reducing parenchymal support, and increasing the surface tension of the lining fluid. All of these changes result in the vicious cycle of gas trapping, hyperinflation, and breathlessness that are the characteristic features of exacerbations of COPD.

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# 3

# Respiratory Mechanics During Acute Respiratory Failure of Chronic Obstructive Pulmonary Disease

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## I. Introduction

Chronic obstructive pulmonary disease (COPD) is associated with profound changes in the characteristics of airways and airspaces. The unevenness of these changes within the lungs determines important abnormalities in ventilation-perfusion matching and impairs gas exchange, as discussed in detail in Chapter 8. From the mechanical standpoint, the hallmark of COPD is expiratory flow limitation, which results from airway narrowing and loss of lung elastic recoil pressure due to chronic bronchitis and emphysema, respectively. Compensatory strategies to airflow obstruction include the increase of inspiratory flow to allow more time for exhalation and hyperinflation to take advantage of higher expiratory flows at higher lung volume. Both mechanisms increase the work of breathing and hence place a burden on the inspiratory muscles (1). Acute respiratory failure (ARF), implicitly occurring on the background of considerable chronic abnormalities, is the result of an imbalance between the constraints arising from the increased mechanical load and the ability of the respiratory muscles to sustain it. The predicament of the respiratory muscles and its consequences are discussed in Chapters 4, 5, and 6.

The focus of the present chapter will be on the role of respiratory mechanics

in the genesis of ARF and on recent advances in the detection of expiratory flow limitation. A detailed description of the theory and clinical assessment of respiratory mechanics during mechanical ventilation can be found in Chapter 29. Several accounts of respiratory mechanics during the various stages of COPD are available (2,3).

## II. Theoretical Considerations

### A. From Expiratory Airflow Obstruction to Increased Inspiratory Load

*Flow-Volume Loops*

Before discussing the origins of the increased work of breathing in ARF of COPD and the corresponding consequences in terms of monitoring and therapeutic strategies (see below), it seems useful to briefly reexamine the process which, from predominantly expiratory disturbances, leads to inspiratory dysfunction and, in the case of ARF, failure.

Expiratory flow is set by the balance between the opposite effects of a positive pleural pressure on the lungs and airways. A positive pleural pressure promotes expiration by deflating the lungs, via chest wall recoil or expiratory muscles contraction. At the same time it also tends to compress the airways. If the structure of the latter has deteriorated as a result of pathological processes, as is the case in COPD (4) (cf. also Refs. 5–7 and Chapter 2), they will decrease in caliber or even collapse when faced with an increase in pleural pressure. When the latter is of sufficient magnitude to offset the flow-driving effect of alveolar pressure, flow limitation occurs. As the disease progresses, flow limitation tends to appear earlier (3), and the range of volume over which flow is independent of effort and depends solely on the passive characteristics of the lungs and airways increases. In COPD, therefore, it is the disease itself that both is responsible for the decrease in maximal expiratory flow and prevents its compensation by an increase in expiratory driving pressure. Compensation of this passive, internal, phasic, and obligatory expiratory mechanical load must therefore come through mechanisms other than expiratory events, as can be seen from analysis of flow-volume loops (Fig. 1).

In a normal subject (left panel of Fig. 1), the loop (solid line) obtained during maximal forced inspiratory and expiratory efforts should define the limits of a "domain" containing all possible flows and accessible volumes. The expiratory limb is roughly triangular, reaching its peak at a lung volume close to 80% of vital capacity (VC) (i.e., near total lung capacity, TLC), whereas the inspiratory limb is approximately semicircular. During resting breathing (dashed line), a very small portion of the maximal domain is used, and inspiratory and expiratory flows always remain far from maximal. Starting from functional residual capacity (FRC), the pattern of breathing can be modified in any direction: by increasing

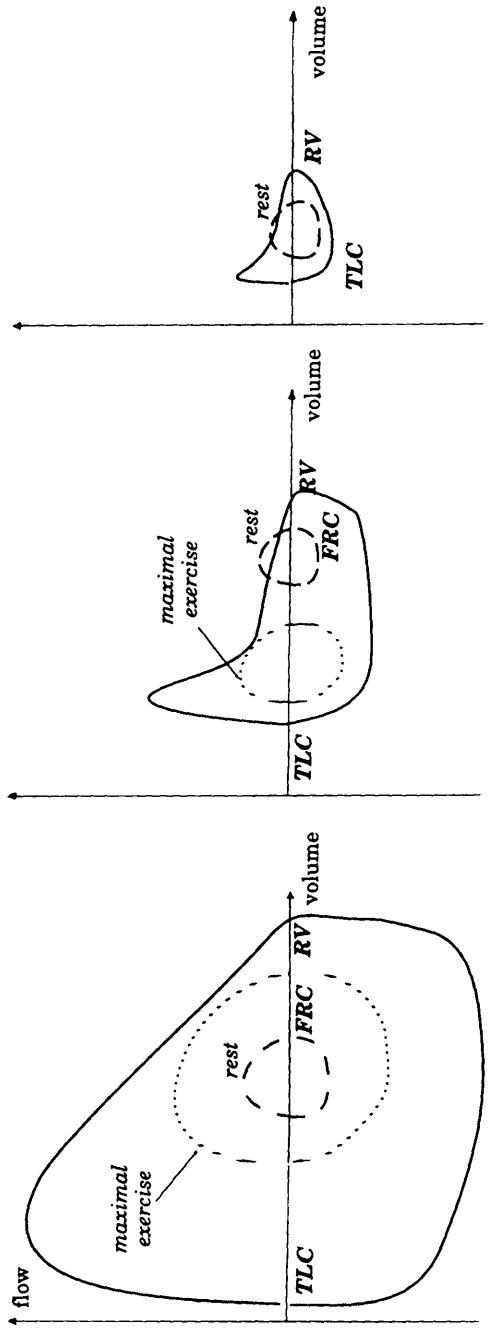


**Figure 1** Schematic representation of flow-volume curves. (Left) Normal subject during resting breathing (dashed line), maximal exercise (dotted line), and a maximal maneuver (solid line). (Middle) COPD patient with severe flow limitation. Note that expiratory flows are higher during a tidal expiration than during the forced maneuver. (Right) COPD patient with acute respiratory failure. See text for details.

inspiratory or expiratory flow, or by increasing or decreasing lung volume. The four strategies are actually used during maximal exercise (dotted line), during which normal subjects start inspiration below FRC (which puts the diaphragm on a better portion of its force-length relationship and makes the elastic recoil of the chest wall available to drive inspiration), increase tidal volume, and produce higher inspiratory and expiratory flows. It can also be seen that even during maximal exercise normal subjects do not reach their maximal flows.

The situation of stable patients with severe COPD is different (middle panel of Fig. 1). The overall shape of the external limit of the maximal envelope is more or less preserved (roughly triangular during expiration with maximal flows reached near TLC and semicircular during inspiration), but the maximal potential area (solid line) is considerably reduced as compared to normal. Mead used this reduction to define respiratory failure (8). The expiratory side of the envelope is predominantly affected. At any given lung volume, forced inspiratory and expiratory flows are reduced, as is forced vital capacity (FVC). During tidal breathing, the inspiratory flows remain smaller than maximal, but the expiratory flows can actually exceed the values obtained at the same lung volume during the forced expiratory maneuver. This reflects the collapsibility of the airways in severe COPD and their compression by the positive pleural pressure produced by contraction of the expiratory muscles. This phenomenon is a general feature of patients with $FEV_1$ smaller than about 1.2 L (9,10), in other words those who are candidates for ARF. In the middle panel of Figure 1 it can be seen that such a patient cannot increase ventilation by increasing expiratory flows, nor by decreasing lung volume. The only available strategy is to increase the inspiratory flow and/or to increase the volume (see next section). Thus, the primary expiratory limitation, which is passive, can only be overcome by an inspiratory compensation, which is active. This implies an increased demand on the inspiratory muscles, which, at increased lung volume, have to operate under disadvantageous force-length conditions and abnormal thoracic geometry (11–14). In ARF (right panel of Fig. 1), in which there is a further reduction of the area subtended by the maximal envelope, tidal breathing occupies half of the maximal flow-volume surface. Under these conditions, compensation may become impossible.

### *Dynamic Hyperinflation and Intrinsic PEEP*

In normal subjects at rest, the elastic recoil of the lung at end-expiration equals that of the chest wall. The end-expiratory lung volume (FRC) therefore corresponds to the relaxation volume (Vr) of the respiratory system, namely the volume at which the elastic recoil pressure of the total respiratory system (Pst,rs) is zero (12,15). Hyperinflation is defined as an increase of FRC above its predicted normal value. This may be due to loss of elastic recoil of the lung, as in emphysema where the end-expiratory volume is increased but the corresponding Pst,rs is still zero; i.e.,

the increased FRC matches Vr. Such a situation is termed "static hyperinflation." By contrast, dynamic hyperinflation corresponds to the situation where FRC is increased because the duration of expiration is insufficient for the deflating lungs to reach Vr prior to the next inspiration, and as a result, Pst,rs is no longer zero but becomes positive. Dynamic hyperinflation is promoted by conditions that impede expiratory flow (e.g., increased airway resistance) or shorten expiratory time (Te) (e.g., increased breathing frequency) (16,17) in absolute or relative terms (an excessive volume to be expired over Te with a given airway resistance will promote dynamic hyperinflation independent of flow limitation; this is of particular importance when setting mechanical ventilation in a COPD patient (see below).

Under normal conditions, alveolar and airway opening pressures at end-expiration are zero. As soon as the inspiratory muscles contract, alveolar pressure becomes subatmospheric and begins to drive gas toward the alveoli (Fig. 2A). If breathing takes place at lung volumes higher than Vr, as a result of dynamic hyperinflation (middle panel of Fig. 1), the Pst,rs at end-expiration is positive. This is termed "intrinsic PEEP" (PEEPi). In such circumstance, the onset of inspiratory muscle activity and inspiratory flow become asynchronous, reflecting the need for PEEPi to be overcome before alveolar pressure becomes subatmospheric (Fig. 2A). This corresponds to an inspiratory threshold load (internal, static, elastic, and obligatory) and increases the static elastic component of inspiratory work (see below) (Fig. 2B).

In spontaneously breathing patients, PEEPi can be estimated as the amplitude of the negative deflection in esophageal pressure, starting from the onset of inspiratory effort and finishing at the onset of inspiratory flow (Fig. 2A). This dynamic PEEPi is generally somewhat lower than static PEEPi, as obtained by the end-expiratory occlusion technique used during mechanical ventilation (18). However, a crucial element for interpreting dynamic PEEPi in a patient is his pattern of abdominal muscle contraction. Contraction of abdominal muscles during expiration is common in ARF and can be very intense (19). Even during quiet breathing, some patients with severe COPD contract the abdominal muscles during the latter part of expiration, and this is principally the case for the transversus abdominis (20). The electrical activity of this muscle correlates with the degree of airway obstruction as assessed by $FEV_1$: in a study by Ninane et al. (20), $FEV_1$ averaged (±SD) $0.81 \pm 0.43$ L in the patients exhibiting expiratory muscle activity, whereas it averaged $1.58 \pm 0.78$ L in the patients in whom the abdominal electromyogram was silent. By contrast, abdominal muscle activation did not correlate with FRC, $PaO_2$, and $PaCO_2$ (20). From the mechanical standpoint, the phasic expiratory activity of the transversus abdominis reduces the anteroposterior diameter of the abdomen and increases the abdominal pressure (21). Transmission of this pressure to the thorax increases alveolar pressure, thereby generating a certain amount of positive expiratory pressure. The latter is clearly different in

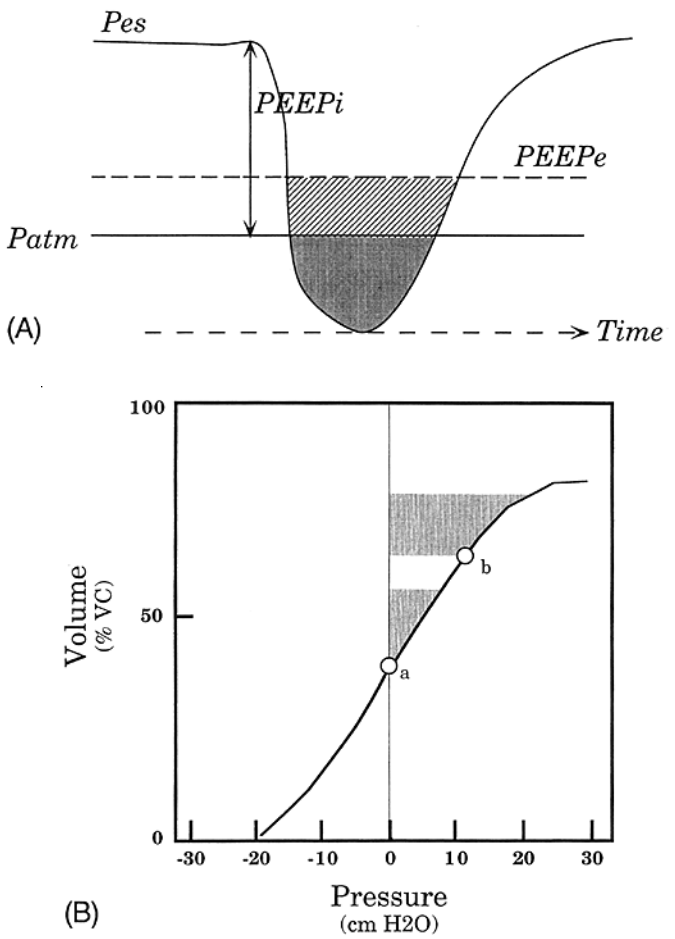


**Figure 2** (A) Schematic representation of a pressure-time diagram in the presence of dynamic hyperinflation. At end-expiration, esophageal pressure (Pes) is above atmospheric pressure (Patm). The first part of inspiration only serves to bring alveolar pressure to Patm, which corresponds to dynamic PEEPi (arrow). The shaded area depicts the fraction of the pressure-time area, i.e., of the inspiratory work of breathing, which actually produces tidal volume. The application of external PEEP (PEEPe) offsets PEEPi and enhances the efficiency of inspiration (hatched area). (B) Static volume-pressure representation of the same phenomenon. When inspiration starts from point b (increased end-expiratory lung volume, namely dynamic hyperinflation), the elastic work of breathing (shaded area) is higher than when inspiration starts from point a (relaxation volume of the respiratory system). VC, vital capacity.

meaning from PEEPi, as Pst,rs is not increased. Nevertheless, it interferes with its measurement. Indeed, in most of the patients studied by Ninane and co-workers (21) in whom the degree of airway obstruction was moderate to severe but who were in stable state, the increase in end-expiratory pressure was entirely due to a rise in Pga. In COPD patients receiving PEEP during ARF, Appendini et al. (22) and Lessard et al. (23) also showed that transmission of gastric pressure to the thorax significantly contributed to the positive end-expiratory alveolar pressure. It follows, therefore, that the determination of PEEPi in spontaneously breathing patients is possible only if the abdominal muscles are not active during expiration. This is seldom the case in ARF, and hence, in this setting, an accurate measurement of dynamic PEEPi requires simultaneous determination of gastric and esophageal pressures. From a therapeutic standpoint, the contribution of abdominal muscle contraction to the rise in end-expiratory alveolar pressure has to be taken into account when offsetting PEEPi by the application of PEEP is considered (see below).

### *Abdominal Muscle Contraction During Expiration*

The reason why COPD patients contract the abdominal muscles during expiration is not clear. It has been postulated that such a contraction may be beneficial because of lengthening of the diaphragm, resulting in improved generation of a negative pleural pressure (better position on the length-tension relationship, better geometrical configuration) (24–26). Indeed, in humans the orientation of the transversus abdominis muscle fibers is favorable for such a mechanism to actually take place (27). However, the electrical activity of the expiratory muscles stops way before the onset of the inspiratory activity of the diaphragm (20), leaving sufficient time for it to return to its initial configuration. As already discussed, flow limitation prevents the contraction of expiratory muscles to be efficient in driving expiratory flow. Another hypothesis can be advanced, namely that a decreased lung volume by means of expiratory activity could reduce the load imposed by dynamic hyperinflation. Indeed, relaxation of the abdominal muscles at the beginning of inspiration should release elastic energy and lower the pleural pressure, independent of any inspiratory muscular activity. This mechanism probably explains why in normal subjects expiratory muscle activity is a common response to inspiratory mechanical loads (28). In the absence of hyperinflation, such a response is appropriate because by reducing end-expiratory lung below Vr it permits partitioning of the work of breathing between inspiratory and expiratory muscles (29).

In flow-limited COPD patients, Ninane et al. (21) observed that the relaxation of the transversus abdominis was associated with a fall in pleural pressure, which paradoxically did not generate inspiratory flow. Based on this observation, it may be argued that in COPD patients abdominal muscle contraction corresponds to an inappropriate vestigial response. In this perspective, the in-

creased energy expenditure resulting from contraction of abdominal muscles would be wasted, and patients contracting abdominal muscle during mechanical ventilation would be considered as "fighting" the ventilator (30). However, there is another hypothesis. The relaxation of abdominal muscle contraction could serve to initiate the fall of pleural pressure, thus sparing the inspiratory muscles from this demanding priming task. Such a mechanism is supported by the recent account of Lessard et al. (23) concerning the use of abdominal muscles during pressure support ventilation with PEEP in intubated COPD patients. In this study, the sudden fall in pleural pressure associated with relaxation of abdominal muscles and the onset of inspiratory muscle electrical activity were found to be synchronous. The contraction of inspiratory muscles, therefore, appeared as having "only" to relay the lowering of pleural pressure initiated by the relaxation of expiratory muscles. In this view, the relaxation of expiratory muscles can have an energy-saving effect for the inspiratory muscles even if it does not bring pleural pressure below zero, i.e., even if it does not reduce lung volume below Vr.

### B. Work of Breathing in COPD Patients with ARF

In 1954, McIlroy and Christie (31) reported that the mechanical work of breathing was increased in stable COPD patients, which they attributed to increased airway and "viscous" resistance of the lung. In subsequent studies, it was suggested that the increased work of breathing in COPD patients was also the result of time constant inequality within the lung, which augments the effective dynamic pulmonary elastance and resistance (32,33). Only later was the importance of PEEPi recognized (34).

#### *Effects of PEEPi on Elastic Work of Breathing*

If inspiration starts from Vr (i.e., if PEEPi is absent) and if static elastance of the respiratory system (Est,rs) is linear over the volume change ($\Delta V$) considered, the static inspiratory work per breath is given by:

$$W_{ist,rs} = 0.5\ E_{st,rs}\ \Delta V \tag{1}$$

With PEEPi, Eq. (1) becomes

$$W_{ist,rs} = 0.5\ E_{st,rs}\ \Delta V + PEEPi\ \Delta V \tag{2}$$

Figure 2B depicts the static elastic work required from the inspiratory muscles to produce the same tidal volume from the relaxation volume and from a higher volume. It can be seen (shaded area) that starting inspiration higher than Vr results in a marked increase in Wist,rs. In the example illustrated by the figure, the hyperinflation-related increment in work of breathing is mainly accounted for by PEEPi, though a decrease in static lung compliance (as reflected by the decreased slope of the static P-V curve at the higher portion of the volume excursion) also plays a small role.

In stable COPD patients, both the resistive and elastic components of inspiratory work are increased due to high airway resistance and hyperinflation. A rapid rise in airway resistance (most commonly due to infection, but at times to bronchoconstriction or mucosal edema consecutive to left heart dysfunction) will cause a further increase in resistive work and may lead to expiratory flow limitation. COPD patients with ARF commonly exhibit flow limitation during tidal breathing (Fig. 1, right panel) and tachypnea, which exacerbate hyperinflation, initiating a vicious circle that can eventually lead to inspiratory muscle failure caused by increased energy demand and decreased effectiveness as pressure generators. The importance of hyperinflation can be gauged by comparison of the values of PEEPi obtained in stable COPD patients and COPD patients with ARF. In stable patients, the highest values of PEEPi are in the order of 7–9 $cmH_2O$ (35–37), while during ARF, PEEPi in general rises to 13–15 $cmH_2O$ (34). During mechanical ventilation, values over 20 $cmH_2O$ have been reported (38).

### *Lung Mechanics in Patients with ARF of COPD*

Relatively few lung mechanics studies have been done in COPD patients with ARF. It is only in the last few years that comprehensive studies performed during the most severe episodes have appeared.

Figure 3 shows the average inspiratory work of the respiratory system ($W_{I,rs}$) and its component in 10 anesthetized and paralyzed mechanically ventilated passive COPD patients with ARF. The corresponding values obtained in 18 normal subjects under the same conditions are provided for the purpose of comparison (39). All measurements were obtained during constant-flow inflation with a tidal volume of 0.73 L, a frequency of 12.5 $min^{-1}$, and an inspiratory duration of 0.92 sec. $W_{I,rs}$ was two times greater in COPD patients than in the normal subjects, the difference being due to an increase of both the static ($W_{ist,rs}$) and dynamic ($W_{idyn,rs}$) components of work. The increase in $W_{ist,rs}$ was due entirely to PEEPi ($W_{I,PEEP,i}$), which represented 57% of the overall increase in $W_{I,rs}$ of the COPD patients relative to normal subjects. In this study, Est,rs was normal, in agreement with Guérin et al. (40) and Tantucci et al. (41), who reported Est,rs values of 10–13 $cmH_2O/L$ in COPD patients with ARF. By contrast, Broseghini et al. (38) found markedly increased values of Est,rs (above 17 $cmH_2O/L$) in similar patients. This discrepancy is probably due to the fact that in the latter study the measurements were done very early in the course of ARF (first day of mechanical ventilation). At this time, the patients exhibited a more marked degree of dynamic pulmonary hyperinflation as reflected by higher values of PEEPi, and as a consequence, their tidal volume excursions probably impinged into the flat part of their static volume-pressure (V-P) curves. Even so, most of the increase of static work was attributable to PEEPi.

In the COPD patients of Figure 3, the increase in dynamic work of breathing, $W_{idyn,rs}$, accounted for 43% of the overall increase in inspiratory work.

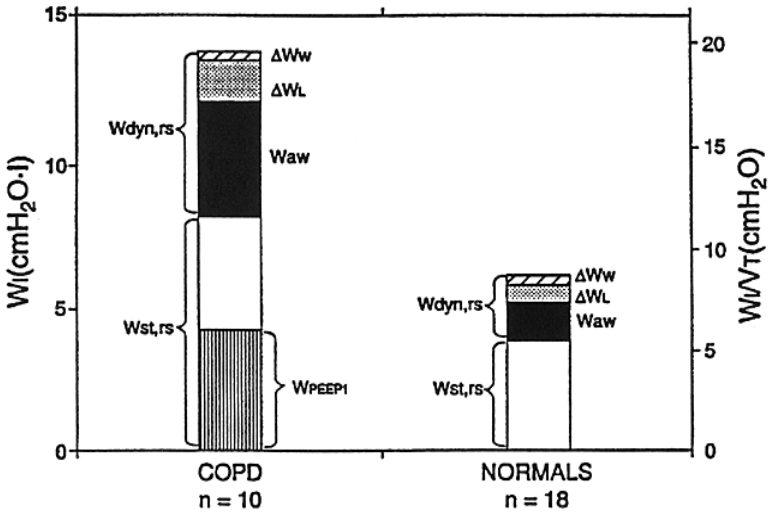


**Figure 3** Average values of inspiratory work ($W_I$) done on the respiratory system and its components in 10 COPD patients and 18 normal anesthetized paralyzed subjects with inflation flow of 0.81 L/sec and tidal volume of 0.73 L. Wst,rs, total static work of respiratory system; $W_{PEEP,i}$, static work induced by intrinsic PEEP; Wdyn,rs, total dynamic work of respiratory system; Waw, airway resistive work; $\Delta W_w$, viscoelastic work of chest wall; $\Delta W_I$, work of lung due to time-constant inequality and/or viscoelastic pressure dissipations. Work per liter of inspired volume ($W_I/V_T$) is shown on the right ordinate. (From Ref. 39.)

Airway resistive work ($W_{I,aw}$) was on average 3.3 times higher than in the normal subjects and contributed 34% of the overall increase in $W_{I,rs}$. The increase in $W_{I,aw}$ in the COPD patients mainly reflects increased airway resistance (Raw). According to Guérin et al. (40) and Tantucci et al. (41), at similar inflation volume and flow, Raw in COPD patients with ARF is about 3.5 times higher than in normal subjects. Values of Raw reported by Broseghini et al. (38) were even higher, again presumably because of the early timing of this study. It should be noted that the four aforementioned studies were based on measurement of tracheal pressure rather than airway opening pressure. Therefore, the corresponding dynamic work done on the endotracheal tubes is not included. This additional work is substantial. In the study of Coussa et al. (39), with endotracheal tubes of 7 and 9 mm internal diameter, it amounted to 4.8 cm $H_2O$/L and 2.0 $cmH_2O$/L, respectively, as compared to 3.8 $cmH_2O$/L for the airways themselves.

In addition to the increased $W_{I,aw}$, the increase in $W_{Idyn,rs}$ was also due to an increase in the "additional work" done on the lung, which will henceforth be

referred to as $\Delta W_{IL}$. $\Delta W_{IL}$ is a consequence of pressure dissipations caused by viscoelastic behavior of pulmonary tissues and/or time-constant inequality (42). There is also an additional dynamic work due to the tissues of the chest wall,$\Delta W_{Iw}$. Values for $\Delta W_{Iw}$ have been found similar in COPD patients (39) and normal subjects (43). The determinants of $\Delta W_{IL}$ in normal subjects and in COPD patients are probably different. As originally proposed by Mount in 1955 (44) to explain the decline in dynamic pulmonary compliance with increasing frequency of breathing, $\Delta W_{IL}$ in normals predominantly reflects the viscoelastic behavior of the lungs, which confers time dependency to the elastic properties (45–47). In COPD patients, however, where the lungs are heterogeneous in terms of time constants, the contribution of gas redistribution to $\Delta W_{IL}$ should be greater (32,39). The latter probably mainly explains the fact that values of $\Delta W_{IL}$ found in COPD patients with ARF were, on average, 2.3 times higher than in normal subjects. Nevertheless, the increase in $\Delta W_{IL}$ represented only 9% of the overall increase in $W_{I,rs}$ observed in the COPD patients (39) (Fig. 3).

Predictably, the increase of $\Delta W_{IL}$ in COPD patients (40) is associated with a more marked time dependency of pulmonary elastance than in normal subjects (46). Figure 4 depicts the relationships of static and dynamic elastance of the lung ($E_{dyn,L} = 1/C_{dyn,L}$) to inspiratory flow obtained at a fixed inflation volume ($\Delta V$ = 0.73 L) in 10 COPD patients with ARF (40) and 18 normal subjects (46). Because the inflation volume was fixed, an increase in inspiratory flow implies a shorter duration of inspiration (Ti). Since inspiratory flow is proportional to 1/Ti, Figure 4 actually depicts Ti dependence of elastic properties (45,48). While $E_{st,L}$ was

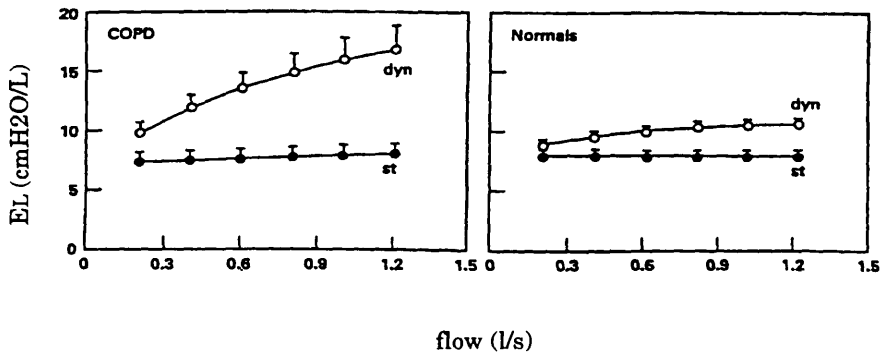


**Figure 4** Changes in average values of static (st) and dynamic (dyn) elastance ($E_L$) of the lungs at constant inflation volume ($\Delta V$ of 0.73 L) delivered at varying inspiratory flow in 10 COPD patients with ARF (left) and 18 normal subjects (right). Because $\Delta V$ was kept constant, increasing inspiratory flow corresponds to decreasing inspiratory time. (From Ref. 40.)

independent of Ti and inspiratory flow in both COPD patients and normal subjects, $E_{dyn,L}$ increased progressively with increasing flow, or, more appropriately, with decreasing duration in inspiration. In COPD patients, the increase in $E_{dyn,L}$ with increasing flow was greater than in normal subjects. This is in line with the fact that in normal lungs the time dependency of pulmonary elastance is due almost entirely to viscoelastic behavior (44,46), whereas in diseased lungs, time constant inequality plays a significant role (32,49). Considering the respiratory system as a whole, the "additional work" corresponding to the effective additional resistance ($\Delta Rrs$) is due to three factors: time constant inequality within the lung, viscoelastic behavior of pulmonary tissue, and viscoelastic behavior of chest wall tissue. In COPD patients with ARF, $\Delta Rrs$ may represent up to 40% of the total resistance of the respiratory system (Rrs) and is substantially higher than normal (38,40,41). It should also be noted that $\Delta Rrs$ is markedly time-dependent, namely that it decreases progressively with decreasing Ti (40,46,48).

Relationships between Rrs and inspiratory flow at fixed inflation volume have been established in both COPD patients (40) and normal subjects (45). Rrs can be partitioned into two components, airway resistance (Raw) and the effective additional resistance ($\Delta Rrs$). Flow has opposite influences on Raw and $\Delta Rrs$: Raw increases approximately linearly with increasing flow, whereas $\Delta Rrs$ decreases according to a roughly hyperbolic relationship. Rrs is higher at low inspiratory flows and decreases with increasing flow, up to 1 L/sec. This value corresponds to a minimal Rrs, because beyond it $\Delta Rrs$ becomes negligible whereas Raw continues to augment. Rrs is about three times higher in COPD patients than in normals at all flows. Also, the pattern of change in Rrs with flow is different at flows higher than 1 L/sec, Rrs tending to increase more steeply in COPD patients. This reflects the preeminence of increasing Raw on the evolution of Rrs at high flow rates. The initial decrease in Rrs with increasing flow represents a clinically important aspect of respiratory mechanics in ARF of COPD because it occurs in the inflation flow range commonly used in the ICU setting (0.5–1 L/sec). Choosing high inflation flow rates should therefore be beneficial both by increasing expiratory time and reducing the inspiratory work done on the respiratory system.

## III. Practical Applications

### A. Measuring and Monitoring PEEPi (see also Chapter 28)

*Rationale*

Detailed reviews of the implications of PEEPi during mechanical ventilation are available (50,51). The existence of PEEPi has many consequences with respect to the care of COPD patients with ARF in the ICU. On one hand, when the patient has to trigger the ventilator to receive mechanical support, be it a volume (assist-control ventilation) or a pressure (pressure-support ventilation), the pressure he

must develop to do so is the sum of the triggering pressure set on the machine and PEEPi (Fig. 2A). If PEEPi is close to the maximal negative pressure that the patient can produce at any given moment, not an uncommon situation in hyperinflated, malnourished COPD patients with ARF where PEEPi can be as high as 20 $cmH_2O$ (38), many or most of the patient's inspiratory efforts will fail to trigger the ventilator (22,52; see also Chapter 29). The corresponding energy waste is at the antipode of the primary aim of mechanical ventilation. On the other hand, when the patient is under controlled mechanical ventilation, all the work of breathing is done by the ventilator. Nevertheless, PEEPi must be taken into account for a correct measurement of respiratory compliance (16), as well as for the interpretation of frequently determined hemodynamic variables such as pulmonary artery occlusion pressure. More importantly, it has adverse hemodynamic effects similar to those elicited by external PEEP (51,53,54), i.e., hampering of cardiac output (55) particularly in the presence of low intravascular volume or impaired myocardial function (56–58). It follows, therefore, that monitoring of PEEPi is necessary in the management of COPD patients with ARF, both to assess correctly the cardiopulmonary parameters and to efficiently counteract the factors that contribute to the development of hyperinflation (59).

### *Detection and Measurement*

Because of the difficulties potentially associated with measurement of dynamic PEEPi (see below), which is the only accessible parameter in spontaneously breathing patients, the available data on PEEPi essentially pertain to patients during controlled mechanical ventilation.

The expiratory flow-time profile, which is now frequently displayed on monitors connected to modern ventilators, provides a simple tool for detection of PEEPi. Normally, i.e., in the absence of dynamic hyperinflation, expiratory flow reaches zero before the next lung inflation. By definition, dynamic hyperinflation is associated with an incomplete expiration: flow persists at the beginning of the next inspiration that abruptly terminates it (Fig. 5). Such a pattern allows the clinician to diagnose dynamic hyperinflation and to ascertain that PEEPi is present. Its precise level is determined by the amount of gas trapped in the lung and the static elastance of the respiratory system.

PEEPi cannot be seen by ventilator built-in pressure-sensing devices, because the latter, being placed within the expiratory line, are essentially exposed to the ambient pressure whenever the exhalation valve is open. Thus, the pressure registered on the ventilator manometer reflects the pressure due to the valve resistance and that of the externally applied PEEP, if present. To assess PEEPi with this manometer, the expiratory port must be occluded at end-expiration (60). This is the reason why PEEPi was initially termed "occult" PEEP (53). After end-expiratory occlusion, alveolar pressure and circuit pressure equilibrate, and hence

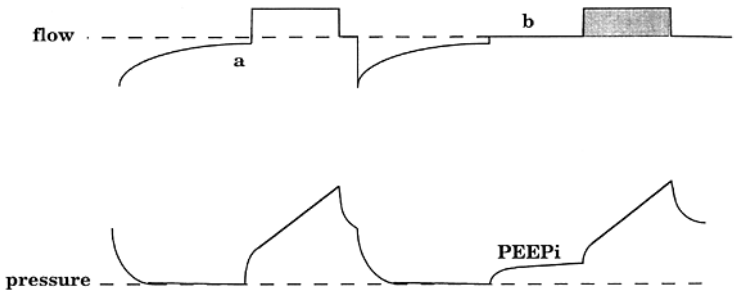


**Figure 5** Schematic representation of flow-time and pressure-time profiles in a mechanically ventilated patient with ARF, with constant flow inflation. (a) Expiratory flow persists until the onset of inspiration, reflecting dynamic hyperinflation. (b) Effect of end-expiratory occlusion (period of zero flow) on the pressure reading of ventilator manometer. The plateau pressure corresponds to static intrinsic PEEP.

PEEPi is seen by the ventilator manometer (Fig. 5). Its reading should be made preferably about 5 sec after valve occlusion, in the absence of respiratory efforts from the patient (61). It should be noted that airway pressure never really reaches a plateau after end-expiratory occlusion, but continues to slowly increase. This reflects viscoelastic rearrangements within the lung and chest wall, a phenomenon known as creep (62–64). The later PEEPi will be read after occlusion, the more it will be affected by this phenomenon.

The end-expiratory occlusion technique described above provides static PEEPi. As mentioned above, static PEEPi is in general higher than dynamic PEEPi. This is because, due to the marked time constant inequality within the lungs that characterizes COPD, PEEPi is not homogeneously distributed. It is higher in units with a slow rate of emptying than in fast ones. During end-expiratory occlusion there is sufficient time for units with different time constants, thus different levels of PEEPi, to equilibrate. Static PEEPi therefore reflects the average end-expiratory elastic recoil pressure of the respiratory system, while dynamic PEEPi should pertain to units with short time constant which start to fill when the slow ones are still emptying. Dynamic PEEPi is therefore the minimum pressure that has to be counterbalanced for inspiratory flow to start.

The degree of hyperinflation can be assessed in terms of volume rather than pressure. To determine the volume trapped in the lungs because of the interruption of passive expiration by the next inspiration, one can insert a prolonged expiratory time at the end of a breathing cycle (generally by transiently setting the frequency of mechanical ventilation to zero) (Fig. 6). Expiratory flow is then allowed to continue until the lung volume corresponds to Vr, i.e., until flow ceases (Fig. 6). Compared to a normal breath, this determines an additional area between the

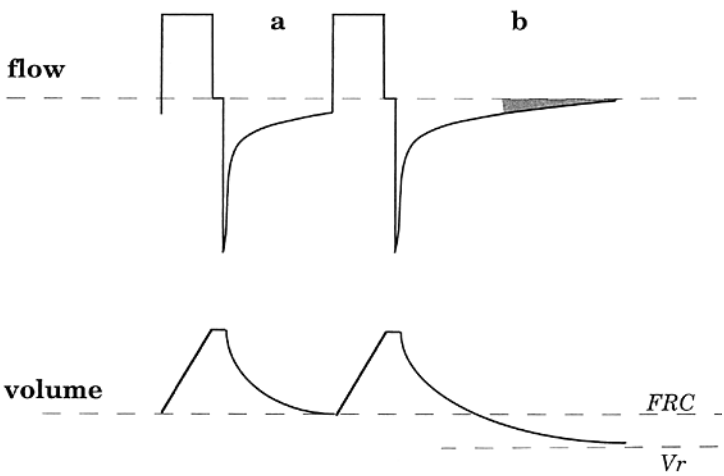


**Figure 6** Schematic representation of the measurement of end-expiratory lung volume. During the breathing cycle (a), dynamic hyperinflation is shown by persistence of expiratory flow until inspiration begins. In cycle b, the duration of expiration has been prolonged by lowering the ventilator frequency and expiratory flow asymptotes to zero (dashed line). The shaded area corresponds to the trapped lung volume, i.e., the difference between functional residual capacity (FRC) and relaxation volume (Vr) on the volume tracing.

expiratory flow curve and the zero line (Fig. 6). It corresponds to the difference between end-expiratory lung volume (EELV) and Vr: $\Delta EELV = EELV - Vr$. Because expiratory flow may be extremely low during the prolonged expiration, the sensitivity of ventilator built-in transducers may be insufficient. Accordingly, measurement of $\Delta EELV$ may be made more precisely by means of a spirometer (57). It is interesting to note that in a study of mechanically ventilated patients with acute asthma, $\Delta EELV$ was linked to prognosis in terms of both morbidity (barotrauma) and mortality (65).

### *Reducing PEEPi or Its Consequences*

Several strategies can be used to minimize PEEPi. External factors promoting hyperinflation include the resistance of the endotracheal tube and of the ventilator circuit. Therefore, intubation should preferably be performed with tubes of large diameter, with length reduced as much as possible. Bronchodilators may be useful in reducing both flow resistance and PEEPi (66–68). During controlled mechanical ventilation, settings should be chosen with the aim of optimizing expiration. This includes reducing tidal volume, decreasing breathing frequency, and preserving the energy available to drive flow. A minute ventilation not exceeding 110–

115 ml/kg/min, with low tidal volume (about 8 ml/kg) and short inspiratory time (hence high inspiratory flows), has been associated with the lowest values of ΔEELV in flow-limited, mechanically ventilated patients (57). Setting an end-inspiratory pause should be avoided when volumetric ventilatory modes are used (69,70), both because it shortens the time available for expiration and because during the pause there is a dissipation of some of the elastic energy that otherwise is available to drive flow (47). When the patient is active and triggers the ventilator, correction of factors that tend to increase minute ventilation (e.g., pain, fever, etc.) or generate tachypnea should be beneficial.

A few points warrant mention. First, for a given level of minute ventilation, a reduction of tidal volume appears to be more efficient in terms of ΔEELV than a reduction in frequency (57,70). Second, the settings proposed above often lead to persistent hypercapnia. The deleterious effects of hyperinflation, however, exceed those of hypercapnia and, to a certain extent, also those of respiratory acidosis. Therefore, decreasing the former by being relatively permissive with the latter appears to be a reasonable strategy (58,69,70). Third, it must be kept in mind that dynamic hyperinflation is not always associated with flow limitation: even with normal airway resistance a large tidal volume and/or a short Te can lead to incomplete expiration. This is particularly important when considering the application of external PEEP to offset PEEPi (see below).

In general, PEEPi can be minimized, but not completely suppressed, by optimizing the ventilator settings in COPD patients with ARF. A further reduction in inspiratory work and associated effort in spontaneously breathing patients can be achieved by offsetting it, at least in part, by application of external PEEP. This approach has been used successfully in stable patients with severe COPD (71,72) and during weaning from mechanical ventilation (73). At present, in line with the waterfall theory of expiratory flow limitation (74,75), all available evidence indicates that the application of PEEP in COPD patients with ARF decreases the inspiratory work of breathing required to ventilate the lungs and the effort to trigger the mechanical ventilators. This has been shown during assist-control ventilation, pressure support ventilation, weaning, and mechanical ventilation applied via an endotracheal prothesis or a face mask (22,72,76,77). The application of positive expiratory pressure in COPD patients is beneficial not only in terms or respiratory energetics, but also from the symptomatic point of view. Indeed, it is associated with decreased dyspnea and increased patient-ventilator synchrony, i.e., with greater comfort (73,76). Whether the application of external PEEP to counterbalance PEEPi has an influence on the duration of mechanical ventilation, on the outcome of weaning, and, in the last analysis, on ICU morbidity and mortality remains to be determined. Although this approach should be used with caution because PEEP can have deleterious effects if not appropriately titrated (21,56,78,79), the available evidence suggests that in patients who exhibit

dynamic hyperinflation due to flow limitation (see below) an external PEEP not exceeding 75–80% of PEEPi is both safe and effective.

### B. Detection of Expiratory Flow Limitation

It has long been suggested that patients with severe COPD, who are flow-limited during exercise, may also exhibit flow limitation at rest, as reflected by the fact that they breathe tidally along or above their maximum expiratory flow-volume curve (2,80,81). Flow limitation at rest is likely to occur in the most severe patients (see above). However, because the conventional method to detect flow limitation based on comparison of maximal and tidal expiratory flow-volume curves (80) is neither feasible in patients with ARF nor reliable (82), there is little information about the prevalence of flow limitation during mechanical ventilation. Nevertheless, assessment of flow limitation appears highly relevant in the management of COPD patients with ARF. For example, flow limitation perpetuates hyperinflation and makes weaning difficult (83,84) by causing increased levels of work of breathing with which the respiratory muscles are unable to cope. It is also a source of breathlessness (85). If not recognized, it can lead to suboptimal use of therapeutic resources (84), such as bronchodilators or application of external PEEP to reduce the work of breathing (see above). The latter is not devoid of potential detrimental effects and should be considered only in the presence of flow limitation (50,86,87). Accordingly, detection of airflow limitation in patients with ARF appears to be of paramount importance.

Originally, assessment of expiratory flow limitation was based on determination of isovolume relationships between flow and transpulmonary pressure (isovolume flow-pressure curves), an approach that is technically complex and time-consuming (2,80,81). In the ICU, comparison of forced and resting flow-volume curves cannot be used because it requires a body plethysmograph (88). Furthermore, it is not very reliable (82). Indeed, the changes in airway resistance and static lung recoil elicited by the maximal inspiration prior to the forced expiratory maneuver (89) and time-dependent lung emptying due to time-constant inequality (90) imply that the magnitude of the flow during forced expiration depends markedly on the volume and time history of the inspiration that immediately precedes it. Since, by definition, volume and time history is radically different during resting breathing and FVC maneuvers, comparison of tidal and maximal flow-volume curves may lead to an erroneous assessment of flow limitation (82). This has been shown in COPD patients, where suppression of the end-inspiratory pause preceding the forced expiration has been shown to result, on average, in a 20–40% increase of maximal expiratory flows in the volume range 10–95% FVC (91). To overcome these technical and conceptual difficulties, several alternative methods have been proposed, such as the removal of external

PEEP if present or the addition of a resistance to the expiratory circuit (17). Recently, Valta et al. (92) and Koulouris et al. (82) have proposed a very simple technique that permits detection of flow limitation in spontaneously breathing patients or during mechanical ventilation. A negative expiratory pressure (NEP) of $-5$ $cmH_2O$ is applied at the airway opening during a single tidal expiration, and the ensuing expiratory flow-volume curve is compared with that of the previous control expiration. If NEP results in a sustained increase of expiratory flow (Fig. 7), there is no flow limitation during tidal breathing. On the contrary, if there is no change in the expiratory flow, or if the change is only transient [reflecting displacement of gas from the expiratory line due to rapid decompression (82,92, 93)], flow limitation is undoubtedly present. Inspection of expiratory flow-volume curves or flow-time relationships, such as displayed by modern ventilators, therefore gives easy access to detection and monitoring of flow limitation during tidal breathing. In COPD patients with ARF (92), it has been shown that expiratory flow limitation can be present over most of the tidal expiration, and that it is associated with PEEPi. In the study of Valta et al. (92), patients with a PEEPi higher than 5 $cmH_2O$ were flow-limited during most of expiration, patients with PEEPi below 5 $cmH_2O$ but above 2.5 $cmH_2O$ were flow-limited over the range of 16–59% of tidal expiration, and patients with PEEPi below 2.5 $cmH_2O$ were not flow-limited. This study also demonstrated that shifting from the semirecumbent to the supine position could aggravate or induce flow limitation. Thus, the NEP

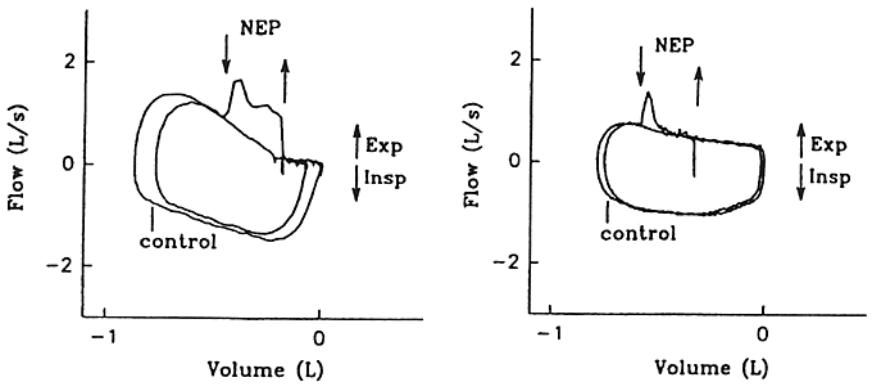


**Figure 7** Effects of a negative expiratory pressure (NEP) on expiratory flow-volume curves. (Left) A breath during which negative pressure was applied over the middle part of expiration in a seated COPD patient, at rest. Compared to the control breath, NEP is associated with a sustained increase in flow, indicating absence of flow limitation. (Right) Similar maneuver in another COPD patient. NEP elicits a transient increase of flow (spike), followed by a rapid return to control values, which indicates presence flow limitation during the control expiration. (From Ref. 82.).

technique should contribute to a better assessment of respiratory mechanics at the different stages of ARF and help to evaluate the impact and usefulness of therapeutic interventions.

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# 4

# Respiratory Muscle Mechanics in Chronic Obstructive Pulmonary Disease and Acute Respiratory Failure

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## I. Introduction

There is no doubt that in chronic obstructive pulmonary disease (COPD) patients the load on the respiratory muscles is increased. Several components contribute to this increased load. Increased airways resistance is commonly present (1). Due to hyperinflation and altered PV characteristics, the elastic load may be clearly increased as well. Finally, the presence of intrinsic positive end-expiratory pressure (PEEPi) in stable COPD or in acute respiratory failure of COPD will substantially enhance the work of breathing (2).

Conversely, the respiratory muscles are usually weakened in COPD patients due to a variety of factors. These include: hypercapnia (3) and hypoxemia (4), cardiac decompensation (5,6), malnutrition (7,8), treatment with corticosteroids (9,10), and electrolyte disturbances (11–14). These factors are responsible for generalized muscle weakness. The inspiratory muscles are further expected to be weakened by hyperinflation (15) and subsequent foreshortening, although powerful adaptive mechanisms at least partly compensate the effects of hyperinflation (16–19).

If the load is increased and the force-generating capacity of the muscles is reduced, then the load faced by the muscles may approach the limits of the

muscles' force-generating capacity or endurance capacity (20). The relationship between load and respiratory muscle strength can be quantified from the ratio of pressure generated per breath to maximum pressure (21), the tension–time index of the diaphragm ($TT_{di}$) (22), the tension–time index of the rib cage muscles ($TT_{rc}$) (23), or the inspiratory effort quotient (IEQ) (24). Normal subjects are unable to sustain esophageal pressures exceeding 40% of maximum, or a $TT_{di}$ greater than 15% of maximum, or a $TT_{rc}$ greater than 30% of maximum, and in patients an IEQ of 0.19 or more is associated with weaning failure (25). Whether the load exceeds the muscles' capacity in COPD patients and the events following such disproportion are addressed in Chapters 7 and 8. The present chapter will focus on the mechanical disproportion itself, i.e., the balance between load and limits of the respiratory muscles. These two factors will be discussed both in stable COPD and in acute respiratory failure of COPD, the subject of the present book. Finally, we will address the alterations in respiratory muscle interaction in stable COPD and in acute respiratory failure of COPD.

## II. Respiratory Muscles in Stable COPD

The load on the respiratory muscles is without question increased in stable COPD patients. Clear increases in airways resistance are usually present dependent upon the degree of airflow obstruction (26,27). Greater elastic work may be present due to hyperinflation and consequent increase in elastic recoil and fall in compliance (28). This effect may be partly offset by an increased pulmonary compliance in emphysematous subjects. Also, PEEPi is commonly present in stable COPD, although it usually only amounts to a few $cmH_2O$ (29–31). Moreover, part of this PEEPi could be due to recruitment of expiratory muscles (32,33). If present, PEEPi acts as an inspiratory threshold load and may increase the work of breathing considerably.

The force-generating capacity of the respiratory muscles as a whole has repeatedly been shown to be reduced in stable COPD patients (19,34–36). This is consistent with data demonstrating reduced oxidative and glycolytic capacity (37) and fiber atrophy in the diaphragm (38), even in the presence of relatively modest airflow obstruction. Oxidative and glycolytic capacity and fiber dimensions of the intercostal muscles appear to be increased, which may signal greater recruitment of the intercostal/accessory muscles (39) (see below).

The factors responsible for the reduction in force-generating capacity of the respiratory muscles are usually assumed to be related to two causes. Hyperinflation is expected to reduce *inspiratory* muscle strength, while generalized muscle weakness will reduce strength of both *inspiratory and expiratory* muscles. While previously hyperinflation was considered to be the major factor weakening the inspiratory muscles, it is now becoming increasingly clear that in COPD patients

generalized muscle weakness is often present and that this generalized muscle weakness has a number of potentially relevant consequences. The causes and consequences of muscle weakness are addressed consecutively.

### A. Hyperinflation

Hyperinflation and its consequences for the inspiratory muscles have been studied repeatedly. Hyperinflation may be severe even in stable patients with functional residual capacity (FRC) frequently exceeding predicted total lung capacity (TLC). Figure 1 shows FRC expressed as a percentage of predicted TLC in 22 emphysematous subjects involved in our pulmonary rehabilitation program. The insert shows the pulmonary function data of these patients. As can be seen, 14 out of the 22 patients have an FRC value exceeding their predicted TLC (15). While potentially beneficial effects may include improved gas exchange, reduced airways resistance (40,41), and allowing for an increase in ventilation in patients who are using maximal expiratory flow during resting ventilation (40), the overall effect of hyperinflation on respiratory muscle function is commonly believed to be detrimental. This is generally thought to result from four factors.

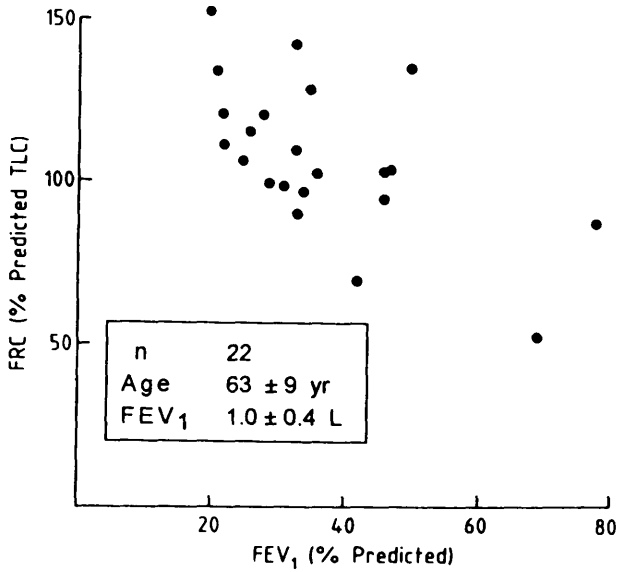


**Figure 1** Functional residual capacity (FRC) expressed as a percentage of predicted total lung capacity (TLC) vs. $FEV_1$ expressed as a percentage of predicted in 22 patients involved in a pulmonary rehabilitation program. Pulmonary function data are shown in insert. (From Ref. 15.)

First, hyperinflation is expected to foreshorten the diaphragm and the other inspiratory muscles and, hence, according to their length-tension properties, to reduce their force-generating capacity. Animal experiments indicate that hyperinflation causes considerable diaphragm shortening (15,42–44) and may therefore curtail diaphragmatic function substantially. Shortening in the other inspiratory muscles, however, is substantially less pronounced (45,46). A similar difference between diaphragmatic shortening and shortening in other inspiratory muscles was found in normal subjects and in COPD patients (47). Although it is still a matter of debate whether parasternal intercostal function improves or remains unchanged (48–50), the inspiratory function of the external intercostals is reduced with hyperinflation (51). The latter muscles, however, retain an inspiratory action over the vital capacity range (51), although this has been disputed by others (52). The fact that intercostal muscle shortening decreases with increases in lung volume will enhance the contribution of intercostal/accessory muscles to chest wall motion, as airflow obstruction progresses (see below).

Second, hyperinflation alters rib cage and diaphragm geometry. Diaphragm geometry is expected to be altered in several ways. The diaphragm may flatten, and according to Laplace's law a greater radius of curvature will be less effective in converting tension generated into pressure (53,54). The relationship between tension generated and pressure, however, may be considerably more complicated than hitherto accepted (55–57). Moreover, hyperinflation is expected to reduce the area of apposition of the diaphragm, and to the extent that the area of apposition is an important feature in the lower rib cage–expanding action of the diaphragm (58–60), it will further reduce the diaphragm's inspiratory action. With severe hyperinflation, paradoxical (inward) motion of the lateral rib cage may occur due to the insertional component of diaphragmatic action (61). Indeed, the diaphragmatic fibers become oriented radially rather than axially, such that their contraction causes inward motion of the lower rib cage.

Third, hyperinflation is expected to alter the mechanical interaction among different inspiratory muscles (59,62). Shifts from parallel arrangements to series arrangements as predicted to occur with hyperinflation by Macklem et al. (59) may fundamentally alter the force output and the capacity to produce displacements of the inspiratory musculature as a whole. Although theoretically and conceptually alterations in mechanical arrangement among inspiratory muscles presumably occur with hyperinflation, and although conceptually an important effect on the global outcome of inspiratory muscle contraction is expected, their effect remains difficult to quantitate.

Finally, severe hyperinflation will move end-expiratory lung volume above the relaxation volume of the chest wall, such that at end-expiratory lung volume inward recoil of the chest wall will be present. This will add to the work of breathing, since the inspiratory muscles will not only work against the lung elastic recoil, but also against the elastic recoil of the chest wall (63).

The alterations in inspiratory musculature occurring with hyperinflation and described above pertain to acute hyperinflation. When hyperinflation is chronic such as in emphysema, the inspiratory musculature is expected to adapt to the chronic foreshortening produced by it. This length adaptation consists of a dropout of sarcomeres and occurs in chronically foreshortened skeletal muscle (64). It was clearly demonstrated to occur in the diaphragm of emphysematous hamsters (16–18). The results of these experiments are summarized in Figure 2. As emphysema and hyperinflation develop, and the diaphragm thus operates at a shorter length, the optimal length shifts to a shorter length as well due to dropout of sarcomeres along the muscle fibers. As a consequence, the match between the optimal length and the in situ operational length is restored. Conversely, the muscle operates at a shorter length with the same degree of filament overlap. This adaptation is of paramount importance in understanding of the effects of chronic hyperinflation on the inspiratory musculature.

Three restrictions, however, have to be made in this context. First, although the sarcomere adaptation is expected to improve inspiratory muscle function, it is not expected to restore the force-generating capacity of the inspiratory musculature completely. Indeed, this adaptation represents an adaptation to the changes in length undergone by the inspiratory muscles, but not to geometrical changes or

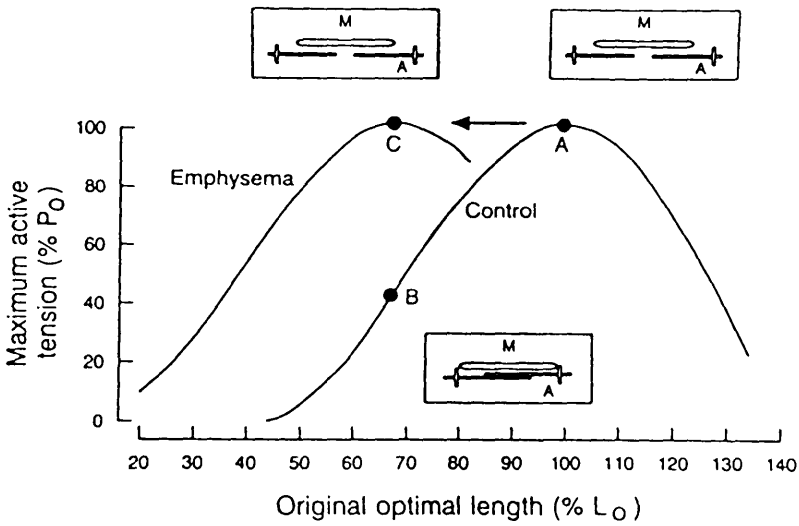


**Figure 2** Shift in the diaphragmatic length-tension curve in emphysematous hamsters compared to control hamsters. Instead of the expected shift from A to B, the shift really occurring goes from A to C. The degree of filament overlap at points A, B, and C is shown. Note that filament overlap is the same at points A and C. (From Ref. 94.)

changes in inspiratory muscle interaction. That this adaptation is incomplete was confirmed experimentally (65). Second, although sarcomere adaptability improves the pressure-generating capacity of inspiratory muscles, it is important to note that it actually reduces the capacity of the diaphragm to produce length changes and, hence, volume changes, since the adaptation reduces the number of sarcomeres in series (66). Thus also in this respect is the adaptation partial. Third, it has been argued whether or not this adaptation occurred in COPD patients (67). The study by Similowski et al. (68), however, almost certainly demonstrates the occurrence of a similar mechanism in humans. Indeed, they demonstrated that although twitch transdiaphragmatic pressure of COPD patients was reduced at FRC in comparison to normal subjects, it was increased for a given lung volume expressed as a percentage of predicted TLC (Fig. 3, upper panel). Figure 3 (lower panel) shows the inspiratory nature of diaphragmatic contraction or the ratio of the fall in esophageal pressure to twitch transdiaphragmatic pressure versus lung volume. This ratio was also clearly greater in COPD patients at a given lung volume. Normalizing lung volume as a percentage of predicted TLC would be appropriate to compare the diaphragm in normals and patients at the same length, if no sarcomere adaptation were to be present. Since force output is consistently greater in COPD patients under these conditions, sarcomere adaptation appears highly likely.

### B. Generalized Muscle Weakness

There is accumulating evidence that muscles are generally weak in stable COPD patients. Figure 4 summarizes data from 23 consecutive patients seen in our outpatient clinic. As can be seen, the vast majority of these patients have a quadriceps force below average normal and even below the lower limit of normality. Expiratory muscle weakness and quadriceps weakness are the reflection of generalized muscle weakness. Evidently, the inspiratory muscles also partake of it. Of the several causes (see above), two are worth emphasizing because they may be highly relevant to stable COPD patients. First, there is accumulating evidence that cardiac failure causes ventilatory (5) and peripheral muscle weakness (6). The former contributes to the sensation of dyspnea (5,69), the latter to the reduction in exercise capacity (6,70). Second, an important role for treatment with systemic corticosteroids in generating muscle weakness in COPD patients has recently been claimed (9,10,71). The evidence supporting this thesis and the histological changes induced in muscles by steroid treatment are expanded upon in Chapter 28.

Two points are worth mentioning. First, there is suggestive evidence that treatment with repetitive bursts of steroids causes muscle weakness even if the average daily dose resulting from such treatment is modest (9,72). Second, muscle weakness may have several consequences in COPD patients. These consequences may include complaints of dyspnea, fatigue, and muscle weakness, reduced

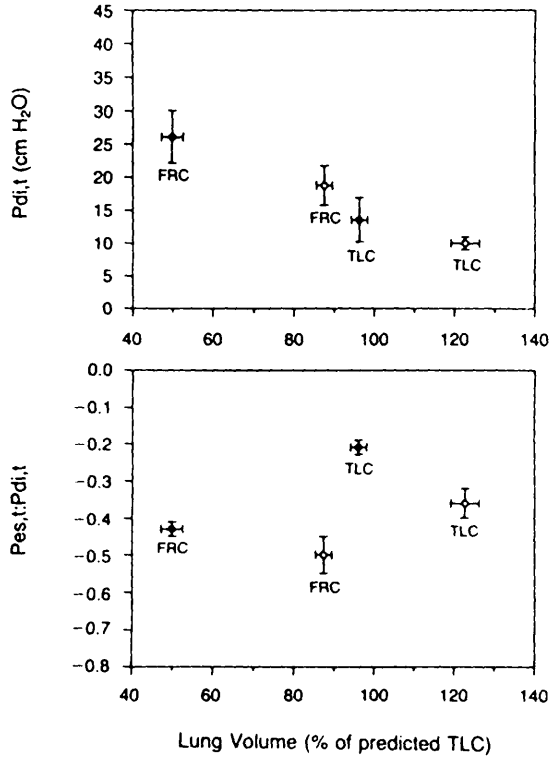


**Figure 3** Twitch $P_{di}$ versus lung volume expressed as a percentage predicted TLC (upper panel), and the ratio of twitch Pes (esophageal pressure) to twitch $P_{di}$ versus lung volume (lower panel). Closed circles, normal subjects. Open circles, COPD patients. Means ± SD. For further explanation see text. (From Ref. 68.)

exercise capacity, enhanced utilization of health care resources, and increased mortality rate. The relationship between complaints of dyspnea and respiratory muscle weakness is well established (69). Limitation of exercise capacity by peripheral muscle function was frequently observed by Killian et al. (73). Recently, utilization of health care resources was found to be related to muscle weakness (74). Interestingly, in a small group of patients with severe steroid-induced myopathy survival was clearly reduced in relation to a control group with a similar degree of bronchial obstruction (75). These consequences require further study in a large-scale clinical trial. If these data were to be confirmed, ventilatory and peripheral muscle weakness would become a matter of primary importance in

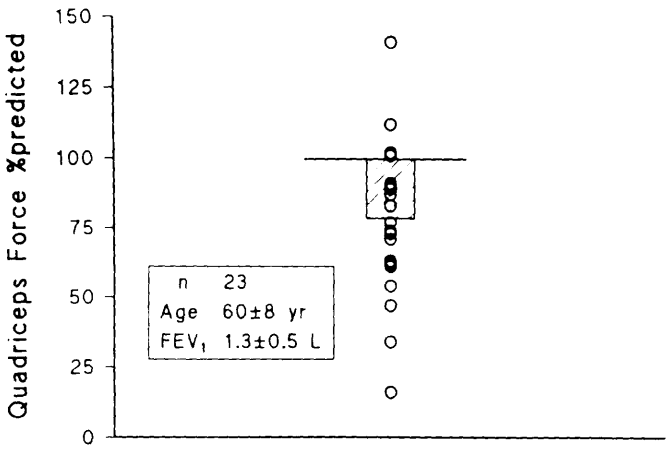


**Figure 4** Quadriceps force (% predicted) in 23 consecutive COPD outpatients. Average normal value and range of normality is indicated by hatched area. Insert summarizes pulmonary function data.

COPD patients. More particularly, the question of whether treatment of muscle dysfunction results in benefits for COPD patients deserves further attention.

## III. Respiratory Muscles in Acute Respiratory Failure of COPD

If the mechanical conditions of a stable COPD patient deteriorate further due to infection, bronchospasm, or cardiac decompensation or other factors, respiratory failure ensues. The load on the respiratory muscles as estimated by a pressure time product under these conditions is clearly much heavier than in the stable COPD patient (1,76,77). Lung or total respiratory system resistance may be enormous in patients with acute respiratory failure, up to 20 $cmH_2O/L/sec$ at a flow rate of 1 L/sec, and lung compliance may be severely reduced, although the reduction is less obvious when PEEPi is taken into account (78). Dead space may be substantial due to ventilation of units with high $\dot{V}/\dot{Q}$ ratio (see Chapter 10). Expiration becomes incomplete due to a severely prolonged expiratory time constant not allowing sufficient time for expiration, and dynamic hyperinflation develops.

Acute hyperinflation developing under these circumstances has two immediate consequences. First, it curtails inspiratory muscle function according to the concepts outlined above. Since hyperinflation develops acutely, there is not sufficient time for adaptations in the respiratory muscles to occur. Second, it enhances the work of breathing since PEEPi up to 20–22 $cmH_2O$ may now be present,

placing an additional burden on the respiratory muscles. Respiratory muscle function may be further curtailed if hypotension develops (79–82). Infection may also contribute to deterioration of respiratory muscle function (79,83). As a consequence, in acute respiratory failure a profound disproportion between load and respiratory muscle capacity is expected to develop. The consequences of this disproportion for the respiratory muscles and breathing pattern are discussed in Chapters 7 and 8.

## IV. Respiratory Muscle Interaction in Stable COPD

In upright humans breathing quietly, chest wall expansion occurs close to the relaxation line (84), due to a coordinated contraction of the diaphragm, parasternal intercostals, and scalenes (85). In the upright position, usually tonic activity in the abdominal muscles is present (86). In stable COPD patients respiratory muscle interaction may be profoundly altered. This is particularly the case if hyperinflation is severe. With increasing airflow obstruction, the contribution of intercostal and accessory muscles usually increases as is evident from the increasing ratio of gastric pressure to pleural pressure swing (87) (Fig. 5) and the decreasing inspiratory expansion of the abdomen (88) (Fig. 6). These alterations point to the reduced contribution of the diaphragm to chest wall motion consequent to its reduced mechanical effectiveness (see above). Paradoxical and asynchronous motion is also variably present in patients with COPD (61,89,90).

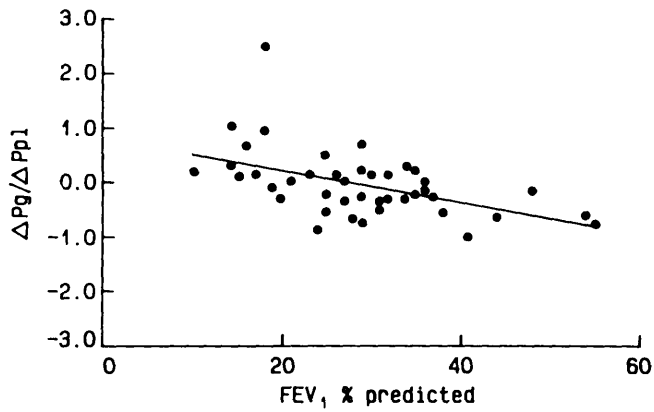


**Figure 5** Ratio ΔPga:ΔPpl in 45 stable COPD patients vs. $FEV_1$ as a percentage of predicted. As can be seen, the ratio increases with increasing airflow obstruction, signaling decreasing diaphragmatic contribution to inspiratory effort with increasing airflow obstruction. (From Ref. 87.)

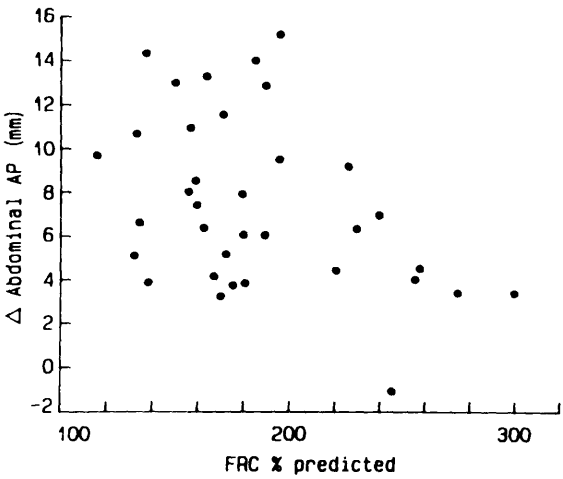


**Figure 6** Change in abdominal anteroposterior diameter during inspiration in patients with stable COPD vs. FRC as a percentage of predicted. As can be seen there is a negative relation between Δabdominal AP diameter and FRC (from Ref. 88), such that in the most severely hyperinflated patients abdominal excursion is severely reduced. Note that the relationship is not very tight.

Shoulder girdle muscles such as the pectoralis major and minor, latissimus dorsi, and serratus are not active during breathing in normal subjects but are regularly activated during quiet breathing in COPD patients (90,91). These muscles have a fixed extrathoracic anchoring point and inflate the rib cage if fixed at this point. They are better recruited when the shoulder is fixed, when the patient leans on a hard surface. Using these muscles for other activities such as combing hair may lead to serious dyspnea in patients who are dependent on them for ventilation. The sternocleidomastoids and trapezii do not appear to be recruited in stable COPD patients, even in the presence of severe airflow obstruction (92).

Another significant alteration in respiratory muscle interaction in COPD patients is recruitment of abdominal muscles. Indeed, these muscles are regularly active in stable COPD patients as is evident from both mechanical (61,87,93) and electromyographic data (32). Relaxation of the abdominal muscles at the onset of inspiration may be associated with inspiratory indrawing of the lower sternum (61). The transversus abdominis is the most frequently recruited muscle. Its recruitment is more frequent with increasing airflow obstruction (Fig. 7). Abdominal muscle recruitment may further contribute to the measured PEEPi (33). This is an important consideration relevant to all studies measuring PEEPi. Indeed, the

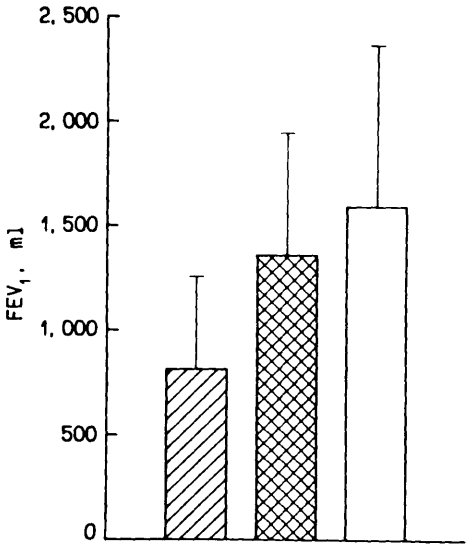


**Figure 7** Relationship between the degree of airflow obstruction and the presence of phasic expiratory activity in the transversus abdominis in 40 stable COPD patients. Mean ± SD. Hatched bars, continuous; cross-hatched bars, intermittent; open bars, absent activity. (From Ref. 32.)

measurement of PEEPi is usually based on the assumption that the expiratory muscles are relaxed. PEEPi is often measured on the esophageal pressure tracing, as the difference in pressure between the beginning of the inspiratory effort, or the beginning of the fall in pleural pressure, and the point of zero flow. If the abdominal muscles are active, then this drop in pleural pressure is not necessarily the result of contraction of the inspiratory muscles, but may also result from relaxation of the expiratory muscles. The presence of abdominal muscle activity thus usually leads to an overestimation of PEEPi. This overestimation is present in stable COPD patients (33). Its relevance in COPD patients in acute respiratory failure still needs to be examined.

The significance of abdominal muscle activity remains poorly understood. Indeed, if flow limitation is present then abdominal muscle contraction will not contribute to expiratory flow, and its relaxation will not contribute to inspiratory flow. This means that the expiratory muscles would then not take up part of the work of breathing, and all of the work of breathing would still be performed by the inspiratory muscles. Abdominal muscle recruitment, however, may still optimize

diaphragm length and geometry under these conditions. These and other potential consequences of abdominal muscle contraction need to be critically assessed.

## V. Respiratory Muscle Interaction in Acute Respiratory Failure of COPD

In acute respiratory failure, dynamic hyperinflation is likely to proceed (see above). Consequently, the effects of acute hyperinflation on respiratory action and interaction are expected to be more pronounced. These include greater ineffectiveness of the diaphragm both as a pressure generator and as a generator of volume displacements, smaller contribution of the diaphragm to chest wall motion and, hence, smaller abdominal displacements, and smaller inspiratory swings in gastric pressure or even inspiratory decreases in gastric pressure (93). Concomitantly, the contribution of intercostal/accessory muscles further increases, enhancing inspiratory rib cage displacement.

In addition, the recruitment of abdominal muscles is also expected to increase. Its contribution to PEEPi measured on the esophageal pressure tracing will be more pronounced. The significance of abdominal muscle recruitment to chest wall motion remains obscure.

## VI. Summary

The respiratory muscles already undergo profound alterations in stable COPD patients. The respiratory muscles are weak due to hyperinflation, which affects inspiratory muscles, and due to generalized muscle weakness in which both inspiratory and expiratory muscles participate. Treatment with corticosteroids may be important in generating respiratory muscle weakness. As a consequence, the inspiratory muscles are less apt to cope with the increased load present in these patients. The load is increased due to an increased airways resistance, a reduced pulmonary compliance, an end-expiratory lung volume exceeding the relaxation volume of the chest wall and the presence of PEEPi.

All of these factors deteriorate in acute respiratory failure. Concomitantly, the force-generating capacity of the respiratory muscles is curtailed due to proceeding hyperinflation, cardiac decompensation, infection, or shock. The disruption of the balance between load and respiratory muscle intrinsic properties further progresses. The events following this disruption are discussed in Chapters 7 and 8.

An important consequence of the alterations described above is that respiratory muscle interaction is profoundly changed. These alterations are already present in stable COPD patients to a certain extent, but they become more obvious in acute respiratory failure. They consist of a reduced diaphragmatic contribution to chest wall motion, an increased contribution of the intercostal/accessory mus-

cles, and progressive recruitment of the abdominal muscles. The functional significance of the latter remains poorly understood.

## Acknowledgment

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# 5

# Role of Respiratory Muscle Dysfunction in Ventilatory Failure

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## I. Introduction

Ventilatory failure is a situation in which the patient cannot sustain adequate gas exchange on his or her own and hence requires mechanical ventilatory support to sustain life. Such failure can originate from either a pulmonary pathology or a neuromuscular pathology. It is the latter situation that will be the focus of this analysis.

Irreversible neuromuscular failure is usually the last stage of a long process, at which point the ventilatory muscles can no longer generate high enough force to sustain an adequate tidal volume, i.e., the ventilatory muscles reached their highest limits of operation. In this chapter two aspects of this process will be reviewed: the concept of the limits on ventilatory muscle function and the role of respiratory muscles on chronic hypercapnia.

## II. Limits of Skeletal Muscle Function

Skeletal muscles are biological structures designed to shorten, and in doing so to generate a given force and velocity. The chest wall is a complex anatomical

structure made of many muscles and billions of sarcomeres and is designed to change the volume of the lungs. The force-generating capacity of the chest wall has been evaluated in terms of the maximal inspiratory and expiratory intrathoracic pressures it can generate against an occluded airway (MIP-MEP). MIP is dependent on the lung volume at which the maximal effort is made. The airflow resulting from a maximal inspiratory effort with an open airway is an expression of the velocity of shortening of the muscles. There are, however, many other functional aspects that can be explored: endurance, EMG behavior, fatigue, etc.

## III. Force-Length Relationship

The classic view of the intricate relationship between structure and function of the chest wall muscles when acting as an inspiratory pump for the lungs was published 75 years ago by Rohrer (1) (Fig. 1). The maximal inspiratory force that can be generated against a closed airway is plotted as a function of lung volume (MIP:VOL) (2). At the lowest lung volume, near residual volume (RV), the inspiratory muscles are at optimal length and seemingly cannot be stretched beyond that point. At the other extreme, the inspiratory muscles cannot expand the rib cage and lungs beyond total lung capacity (TLC), and their effective force at TLC is that required to overcome the elastic recoil of the lungs and the chest wall impedance. The expiratory muscles shown on the right side of Figure 1 reach an optimal length near TLC and cannot be stretched beyond it. Near RV they become short and are ineffective in expelling further air from the lungs because their force becomes equal and opposite to that of the outward elastic recoil of the chest wall. Notice that force varies as a function of age and sex. The version of the MIP:VOL diagram introduced by Campbell (3), adding to Figure 1 the elastic recoil of the lungs, served as a useful tool in considering the limits of maximal respiratory muscle force development and became the basis for a graphical analysis of work of breathing.

## IV. Force-Velocity Relationship

A complementary description of the limits of muscle function is given by the force-velocity relationship, which is an expression of the contractile properties of the sarcomere. Velocity is equated with airways flow, a useful approximation. The maximal inspiratory flow-pressure diagrams of the chest wall were described in 1960 by Agostoni and Fenn (4) (Fig. 2). In practice the force-velocity ratio for a single muscle fiber differs from the pressure-flow relationship of the chest wall. The graph of inspiratory mouth flow (V) to alveolar pressure (Palv) in human subjects is best fitted by a linear regression equation, while in small muscle bundles of rat diaphragm the force-velocity is curvilinear. These differences are

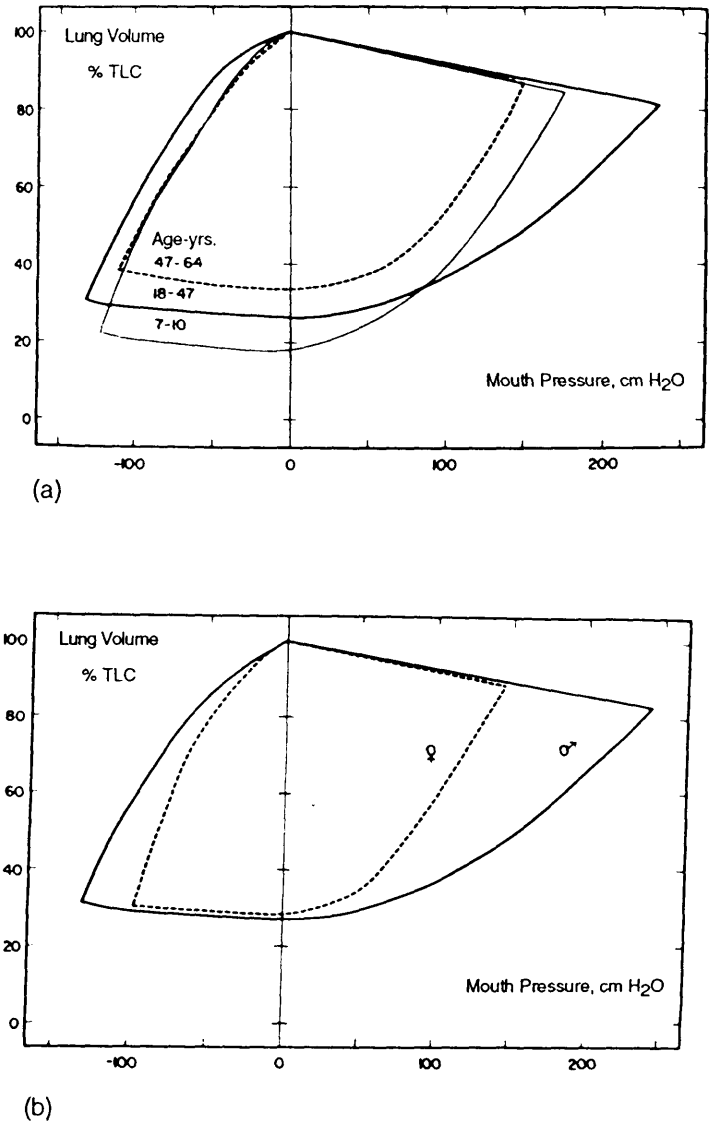


**Figure 1** Lung volume plotted against alveolar pressure during maximum static inspiratory (left) and expiratory efforts (right) against an occluded airway. Values are given for several age groups (a) and for men and women (b).

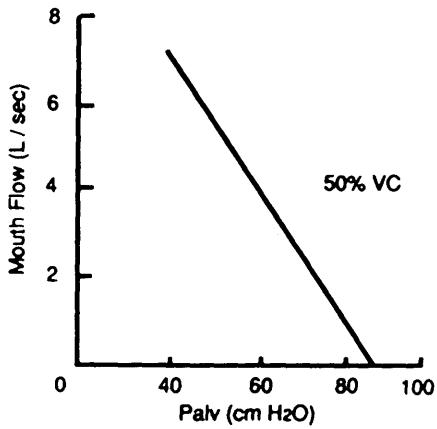


**Figure 2** Relationship of maximal inspiratory flow to alveolar pressure obtained at 50% of vital capacity (VC). (From Ref. 4.)

likely to be attributable to the restriction of the functional range of shortening of the inspiratory muscles determined by their rib cage attachments and the variable load imposed by elastic recoil of the lung and the resistance of the airway.

The MIP/VOL and MIP/V diagrams, despite their usefulness, have limitations as indicators of inspiratory muscle function; they remain a two-dimensional description of a multidimensional system.

## V. Interaction of the Force-Length-Velocity Vectors

If the force (expressed as percent of maximal), length (expressed as percent of lung volume), and velocity of inspiratory muscle shortening (expressed as percent of maximal mouth flow) are plotted on a Cartesian three-dimensional diagram, we obtain a more complete, albeit more complex view of the maximal limits of inspiratory muscle performance.

The maximal limits are indicated by the outer thick lines, or shell, in Figure 3. The space limited by the thick lines, the outer surface linking them, and the three planes of the diagram represent the maximal limits of all possible combinations of flow ($\dot{V}$), pressure (P), and volume (V) that can be achieved. The MIP/VOL diagram (Fig. 3, left panel) shows the maximal force obtained from near isometric contractions at lung volumes from FRC to TLC and corresponds to Figure 1. Values of the parameters plotted on the right panel include peak velocity of shortening (maximal inspiratory flow) that can be achieved at a given lung

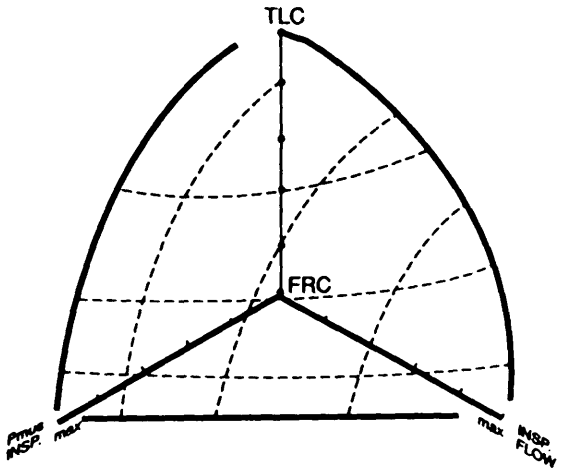


**Figure 3** Relationship between lung volume (FRC-TLC) maximal static inspiratory pressure (Pmax.insp.max), (left panel); lung volume and maximal inspiratory flow (right panel) and Pmus ins - max insp flow. Thick outer lines in all the panels describe the limits of maximal inspiratory effort.

volume as shown in Figure 2. The MIP/flow relationship (force-velocity) is shown at the base of the diagram as a straight line, following Agostoni and Fenn (4) data.

On each of the three peripheral corners of the diagram there are severe limitations in muscle performance. For example, a short inspiratory muscle length (near TLC) constrains P and $\dot{V}$ development; this is the area in which patients with severe COPD operate. On the right corner, high $\dot{V}$ is constrained by the level of pressure available in a rapidly shortening muscle. On the left corner, maximal force can be developed only if there is no change in lung volume. The fourth corner (in the center of the figure) shows length at FRC (optimal), zero force developed by the muscles (rest), and zero flow. This is the point from which actual breathing starts in a normal subject, and it offers the largest number of optional pathways to achieve ventilation. In this diagram, breathing is a tridimensional vector that begins in the center of the figure and moves into the space limited by three panels.

An inspiration held against high resistance, similar to that used experimentally in the studies of inspiratory muscle fatigue by Roussos and Macklem (5) and Bellemare and Grassino (6), is shown projecting on the left panel along a high resistance isopleth. Flow is small, as is tidal volume (VT), but inspiratory pressure is high. The line extending from peak pressure to the outer limit is an expression of

the force still available, termed the force reserve by Bellemare and Grassino (7). The perimeter of the loop projecting mainly on the right panel indicates the course followed in time by the vector observed during hyperpnea, as in exercise; it follows the low-resistance, high-flow, large shortening path. Note that an inspiratory flow of about half maximal results in a small force reserve shown as the distance between pressure at peak flow and the MIP available at that flow (thick volume-pressure line). Although not shown in the figure, if an inspiratory resistance is added, the loop will pivot towards the left-side panel, and if flow is to be maintained, pressure will increase; VT will be limited, and $\dot{V}$ will decrease.

The outer boundaries of function represent a very useful reference parameter. In real life they are seldom reached, except when breathing intentionally for the purpose of measuring maximal force or velocity. Even then, maximal values can be sustained for only a few seconds because activity at these levels results in rapid fatigue and failure of the inspiratory muscles. In real life, breathing evolves within a fraction of the maximal limits known as the maximal sustainable force by Nickerson and Keens (8), maximal sustainable ventilation (MSV) by Tenney and Reese (9), or maximal sustainable tension time (fatigue threshold) by Bellemare and Grassino (6).

## VI. Limits of Respiratory Muscle Endurance

Task failure is a term used to define the failure to keep a pre-imposed breathing pattern. Task failure can occur because lack of the subject's will to continue, because central neural failure or inhibition, because the neuromuscle junction fails or because the muscle fatigues i.e. its performance is impaired. Time to task failure is known as endurance. Hypercapnia is an evidence of failure to maintain adequate alveolar ventilation. There are two major examples of breathing patterns leading to failure:

### A. High Ventilation–Low Impedance

Tenney and Reese (9) pointed out that maximal ventilatory capacity (MVC) can be sustained for less than a minute, while a ventilation of approximately 5% MVV can be sustained for a lifetime (i.e., resting breathing). Somewhere in between there is a ventilation value that can be sustained (MSV) for a finite period (hours), for example, marathon running or a heavy inspiratory load. Sustainable ventilation implies that respiratory muscles do not develop failure in such task. Maximal sustainable ventilation for about 1 is 60–75% of maximal ventilation (10,11). Body exercise never elicits a ventilation equal to MVV in normal subjects. The highest ventilation achieved during sustained exercise, for example, while running a marathon or during cross-country skiing, is about 60% of MVV.

### B. Low Ventilation–High Impedance

Roussos and Macklem (5) measured maximal sustainable transdiaphragmatic pressure (Pdi) in normal subjects breathing against high inspiratory resistances, at slightly above resting values of ventilation, and inspiratory flow of about 0.6 L/sec. They found that a Pdi of up to 40–50% of $Pdi_{max}$ could be sustained for longer than 1 hour without task failure, and they termed this value the critical pressure. Pdi values near 90% of $Pdi_{max}$ were sustained for less than 1 minute. Nickerson and Keens (8) found that maximal sustainable inspiratory pressure was about 70% of MIP. Bellemare and Grassino (6) observed that the maximal sustainable Pdi is variable, depending mainly on the duty cycle (Ti/TT). Breathing with a Ti/TT of about 0.4 (normal), the maximal sustainable pressure was about 40% of maximum. Higher and lower Ti/TT resulted in lower and higher sustainable Pdi values, respectively.

The concepts of maximal and sustainable limits of pressure and flow at various lung volumes are illustrated in Figure 4, in which the axes are those shown in Figure 3, representing lung volume, inspiratory pressure, and inspiratory flow. The outer boundary of this igloolike structure shows the maximal limits within which breathing maneuvers can be held (Fig. 5). The smaller "igloo" inside is the space within which sustainable force and the corresponding flow can be held if the breathing pattern is held constant at a Ti/TT of 0.4. It shows that if breathing is held against inspiratory resistances with negligible flow, up to 40% of the maximum force can be held. If the hyperpnea pattern is held, about 40% of maximum flow can be held if inspiratory resistance is small. The shaded triangular area represents the limits within which sustainable (or nonfatiguing) patterns can be held. A hypothetical breath vector is shown as a full line starting at the FRC corner. Pressure, flow, and volume increases follow the direction of the arrow to the end of inspiration at zero flow, when pressure is equal to the elastic recoil of the lung.

The upper triangles in Figure 5 represent smaller nonfatiguing areas that are available if inspiration starts at higher lung volumes. There, the breathing pattern becomes limited in terms of the available VT, pressure, and flow, regardless of the extent of muscle activation. The values given in Figure 5 are semiquantitative and based on the information available. The main purpose is to show the maximal and sustainable "spaces" or degrees of freedom of inspiratory muscle function.

## VII. What Makes the Respiratory Muscles Stop Working Adequately?

The respiratory muscle becomes unable to sustain ventilation (mechanical failure) as the progressive deterioration of its function occurs, a process called "fatigue."

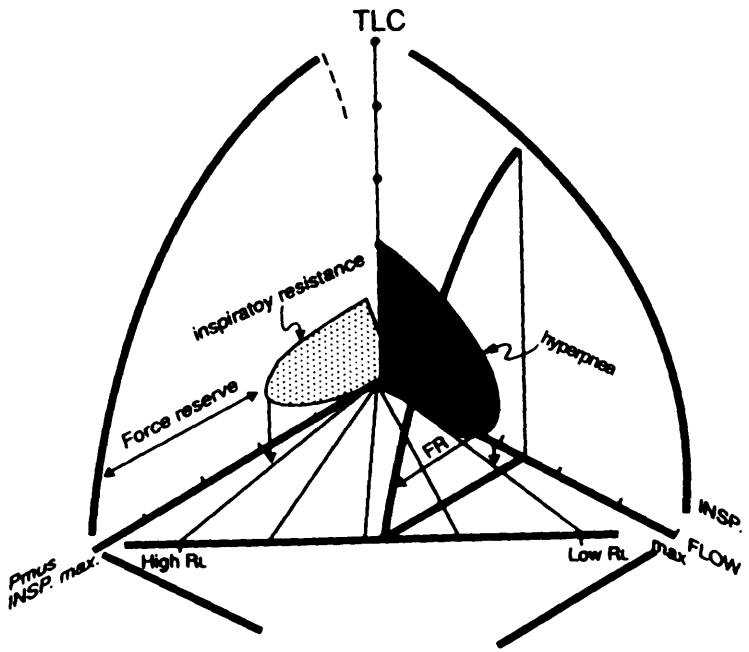


**Figure 4** Same axes as Fig. 3. The pointed area on the left panel describes the time course of an inspiration held against high inspiratory resistance. The block loop depicts an inspiration held at high flow and low resistance as in hyperpnea. Isopleths on the base panel are isoresistance.

It includes changes in the molecular aspects of the muscle (insufficient ATP to drive the intra/extracellular movement of calcium from the sarcoplasmic reticulum, changes in the enzymatic processes due to changes in intracellular pH, accumulation of oxygen radicals, etc.), membrane changes (slow propagation of electrical potentials, alterations in channel function, particularly $Ca^{2+}$ and $K^{+}$ channels), changes in the cell environment, such as the amount of blood flow to the muscle, and nutritional aspects such as glycogen, heart function, hemoglobin, and gas exchange in the lungs. Since not all of the muscle fibers have the same contractile and metabolic properties, some fail before others (fast fatiguable vs. fatigue-resistant fibers). Thus, the fatigue process is a progressive one, with some fibers within the diaphragm "dropping out" before others, ultimately leading to the gradual loss of force. Fatigue is reversible within hours, if rest is allowed (12). On the other hand, damage to the muscle fiber structure occurs during fatigue and, if sustained long enough, may take days or even weeks to recover and may even produce irreversible loss of force.

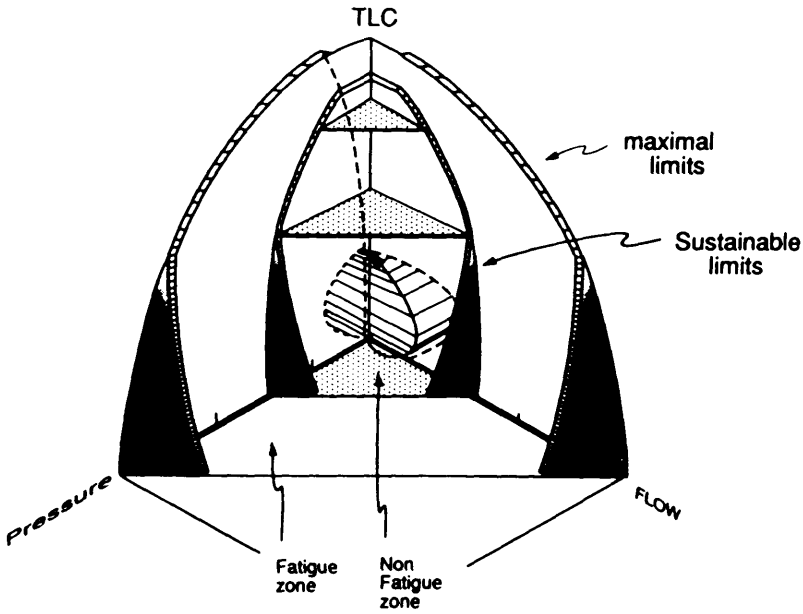


**Figure 5** The outside "walls" are as in Figure 4, and represent maximal limits of flow ($\dot{V}$), pressure (P), and volume (V). The smaller "igloo" represents maximal values of sustainable pressure and flow at various lung volumes, if Ti/TT is 0.4.

## VIII. Chronic Hypercapnia as an Index of Respiratory Muscle Dysfunction

Ventilatory failure is conventionally defined as a higher than normal level of $Paco_2$. The primary task of the cardiopulmonary system is to transfer $O_2$ from the atmosphere to the cells at a rate commensurate with their aerobic requirements and to eliminate the $CO_2$ derived from cellular metabolism into the atmosphere. To maintain a steady state, $CO_2$ removal by the lungs must equal $CO_2$ production ($\dot{V}co_2$). Thus, $\dot{V}co_2 = \dot{V}A \times FAco_2$, where $\dot{V}A$ is ventilation of perfused alveoli and $FAco_2$ is the fractional concentration of $CO_2$ in these alveoli. Rearranging and converting $FAco_2$ to alveolar partial pressure, and substituting $Paco_2$, which is in equilibrium with alveolar partial pressure, gives:

$$Paco_2 = \frac{\dot{V}co_2(BP - 47)}{\dot{V}A} K \qquad (1)$$

where BP is barometric pressure (in mmHg) and vapor pressure equals 47 mmHg. $\dot{V}co_2$ is in ml/min at standard temperature and pressure, dry; VE is in L/min at

body temperature and pressure, saturated; when BP equals 760 mmHg, a constant K of 0.863 mmHg emerges.

The ventilatory system normally responds vigorously to any increase in $\dot{V}CO_2$ (13) or in $PaCO_2$ beyond normocapnic levels (14) by increasing ventilation ($\dot{V}E$). Only the fraction of $\dot{V}E$ that remains after allowing for dead space to tidal volume (VD/VT) is useful for $CO_2$ exchange, as shown in the following equation:

$$PaCO_2 = \frac{\dot{V}CO_2 \cdot K}{\dot{V}E(1 - VD/VT)} \tag{2}$$

Among the determinants of $PaCO_2$, the VD/VT was consistently found to be increased in hypercapnic COPD patients in the steady state, while $\dot{V}CO_2$ and $\dot{V}E$ changes were inconsistent (15–17). This in no way identifies the increased VD/VT as the "culprit" in hypercapnia, taken as evidence of failure. Although alveolar ventilation is low in relation to $CO_2$ production in hypercapnic patients, $CO_2$ removal and $O_2$ intake by the lungs are usually normal or even enhanced in the steady state. Hence, the primary goal of the respiratory-circulatory system is achieved. As for the slightly increased $\dot{V}CO_2$, the compensation for the levels of VD/VT found in hypercapnic patients could easily be achieved by the normal ventilatory apparatus. Indeed, virtually all diseases that ultimately result in hypercapnia are associated with abnormal respiratory mechanics.

## IX. Respiratory Muscles and Chest Wall Dysfunction in the Genesis of Hypercapnia

Inspiratory muscle force reserve can be reduced drastically when inspiration is impeded and inspiratory muscle strength is reduced (18,19). The principal abnormality in obstructive diseases is narrowing of the airways due to intrinsic disease or reduced pulling out of the airways by lung parenchyma. In addition, a higher dead space–to–tidal volume ratio increases the ventilatory requirements to maintain normocapnia [see Eq. (2)]. Furthermore, expiratory flow limitation leads to dynamic hyperinflation with increased lung elastance, threshold loading from intrinsic PEEP, and reduced pressure-generating capacity of inspiratory muscles (20). Finally, nutritional factors are often operative, with undernutrition reducing inspiratory muscle strength (21) and obesity increasing the $O_2$ consumption per liter of ventilation (22) via mass loading, with a reduction in lung volume with higher inspiratory resistance and more severe expiratory flow limitation. Begin and Grassino (19) explored the correlation between lung resistance, airways dead space, airflow limitation, and inspiratory muscle force reserve in COPD patients in the steady state and their resting $PaCO_2$. Total lung resistance (RL) was found to be a major determinant of the mean intrathoracic pressure swing developed during inspiration (Pi) at rest ($r = 0.85$). $Pi_{max}$ was found to improve the predictive value

of RL and Pi for $Paco_2$, with $RL/Pi_{max}$ the best predictor ($r = 0.57$). A multiple regression analysis related $Paco_2$ to a combination of inspiratory loads [lung resistance (RL), VD/VT, weight (% pred), dynamic lung elastance] and to $MIP_{max}$ ($r = 0.69$), limiting the force reserve, as shown in Figure 6. It was suggested that hypercapnia may be one strategy available to avoid overloading of the inspiratory muscles leading to fatigue and possible irreversible ventilatory failure.

To assess the relationship between inspiratory muscle loading and $Paco_2$, we developed the ventilation equation to include the mechanical determinants of $Paco_2$. Ventilation was expressed as the product of fractional inspiratory time (Ti/Tt) and mean inspiratory flow (Vt/Ti). In turn, Vt/Ti was defined as Pi/Z, where Z is mechanical impedance. Therefore,

$$Paco_2 = \dot{V}co_2 \frac{Z/(1 - VD/VT)K}{Ti/Tt \cdot Pi} \tag{3}$$

This equation is relevant because it relates $Paco_2$ to an index of energy demands of the inspiratory muscles, the pressure-time product (often called tension-time or TTi). The equation states that, for a given $Paco_2$, the inspiratory pressure requirement is directly proportional to the product of $CO_2$ production rate and the ratio of

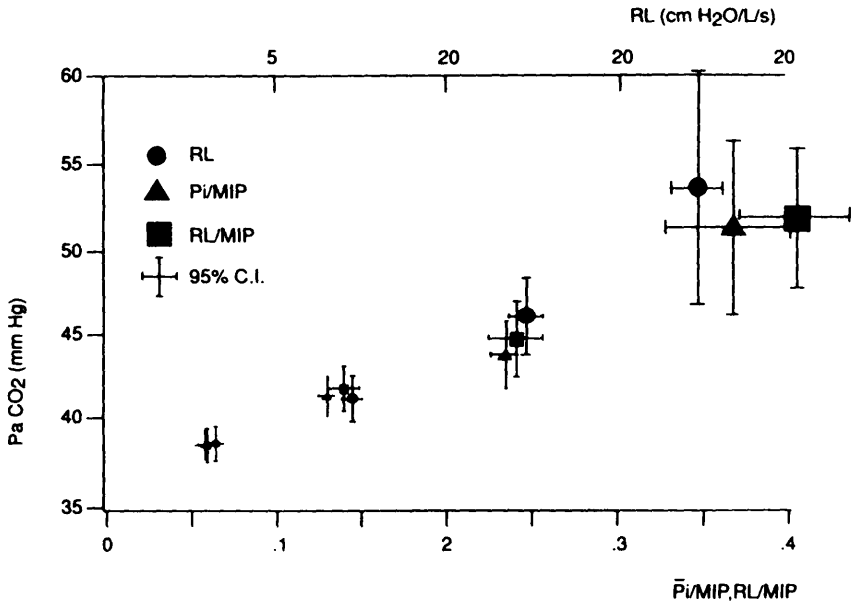


**Figure 6** Relationship between $Paco_2$ and RL/MIP.

mechanical impedance to $CO_2$ ductance (which gives a load with pressure units). This formulation brings in the concept that inspiratory muscle capacity to generate force may limit $CO_2$ washout and be a cause of increase in $Paco_2$. Indeed, we found the highest degree of correlation for $Paco_2$ when considering all the parameters of the numerator of Eq. (3) together ($r = 0.63$).

Equation (3) states that the pressure-time product of inspiratory muscles varies reciprocally with $Paco_2$ when the numerator is kept constant. This is not likely to be the case when hypercapnic patients try to achieve normocapnia. Hyperventilation increases the energy demands of the inspiratory muscles (23), thus $\dot{V}co_2$ increases. In addition, the ability to decrease $Paco_2$ varies as a function of the perfusion of the lung regions overventilated during the maneuver (13). Finally, mechanical impedance is modified with increasing tidal volume and frequency of breathing leading to dynamic hyperinflation (24).

To take into account specific mechanical characteristics of the system, including the volume-dependant variations of alveolar ventilation with inspiratory effort, we expressed the inspiratory pressure requirement for ventilation using a three-dimensional monocompartmental mechanical analog and divided dead space into anatomical or "serial" and alveolar or "parallel" portions. This led to:

$$Paco_2 = \frac{(\dot{V}co_2 \cdot Tt)(R + [Eti/2])(VT - Vdan)/VA\ k}{Ti(Pi - Pthr)(1 - Vdan/VT)} \tag{4}$$

This equation states that $Paco_2$ varies reciprocally with the inspiratory tension-time in excess to a pressure threshold (Pthr = intrinsic PEEP) and to the tension-time required to overcome a volume threshold (Vdan). However, the elastic load (Eti) is seen to increase as inspiration proceeds, reducing the efficiency of the inspiratory muscles to generate alveolar ventilation and to decrease $Paco_2$ at higher lung volumes when maximal sustainable tension-time is approached, inspiratory flow and tidal volume may be limited (see Fig. 3), and hypercapnia may ensue. We acknowledge several limitations of the model. First, resistance and elastance of the respiratory system and inspiratory flow are known to vary as inspiration proceeds. Second, forces dissipated through the chest wall cannot be directly assessed during spontaneous breathing. Third, the expiratory events leading to PEEPi and inspiratory threshold loading, such as expiratory flow limitation, are not included. Fourth, lung inhomogeneity, an important determinant of dead space ventilation and expiratory flow limitation, is not considered. Nevertheless, this analysis provides a conceptual framework that permits us to see the influence of several breathing cycle parameters, either individually or in combination. For instance, it provides a rationale to explain the occurrence of hypercapnia (6) and low ventilatory response to $CO_2$ and exercise in COPD patients on the basis of mechanical impairment and inspiratory muscle loading.

## X. Conclusions

Respiratory muscles form a complex system often explored by following the behavior of parameters linked to their structure (e.g., length) or function (e.g., force, velocity, perfusion, EMG, cellular pH, metabolites, fatigue). Inspiratory muscles can be exerted to their maximal limits during situations such as high ventilatory demand (as in exercise) or low ventilation with high force demands (as in obstructive or restrictive lung diseases). In either circumstance, the level of sustainable activity (many hours) seems to be about half of the subject's maximal ventilatory capacity (MVC) or their maximal inspiratory pressure (MIP), respectively.

Under conditions of muscle dysfunction, even resting alveolar ventilation is compromised and chronic hypercapnia develops. It seems likely that respiratory muscle dysfunction plays a role in hypercapnia. In fact, the natural history of chronic hypercapnia in COPD or in neuromuscular disease suggests that spontaneous ventilation is set at a level below the one at which neuromuscular fatigue will develop, even if this results in "chronic ventilatory failure." When patients suffer a pathology that further decreases their global respiratory muscle function (hyperinflation, malnourishment, etc.) or increases their load, we have the making of a ventilatory failure of neuromuscular (rather than lung) origin.

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# 6

# Respiratory Muscles
## Fatigue

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### I. Introduction

The clinical importance of respiratory, chiefly inspiratory, muscle fatigue has become well recognized during the last 15 years. If inspiratory muscles fail, so do ventilation and tissue respiration. Neuromuscular fatigue had previously been defined as the inability to maintain the required or expected force or power output that follows a sustained muscular contraction and is reversible by rest. In this regard, fatigue of the inspiratory muscles had been defined as the inability to continue to generate sufficient pressure for an adequate alveolar ventilation. Recently the definition of muscle fatigue has been revised; it is defined as a condition in which there is a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load and reversible by rest (1). According to this definition, fatigue may be present long before the point in time at which a muscle is unable to continue to perform a particular task (exhaustion or task failure). In applying this concept to the inspiratory muscles, one concludes that they may be fatigued before there is hypercapnia (task failure) due to inadequate alveolar ventilation. Furthermore, it is now clear that during fatigue from dynamic contractions, the maximum force and velocity of shortening often change independently, whereas previous definition implied that force and

power output necessarily change in parallel. Fatigue should be distinguished from muscle weakness, which is defined as a condition in which the capacity of a rested muscle to generate force is decreased (1), although the presence of such muscle weakness may predispose to muscle fatigue.

Although considerable work has been done, the site and mechanism of fatigue have remained a subject of controversy over the last century. Theoretically, the site of fatigue may be located at any link in the long chain of events involved in voluntary muscle contraction leading from the brain to the contractile machinery (brain, spinal cord, nerve, neuromuscular junction, muscle cell membrane, transverse tubular system, calcium release, actin-myosin activation, and cross-bridge formation) (Fig. 1). Globally, fatigue is distinguished in failure to generate force because of a reduced central motor output (central fatigue) and failure to generate force because of fatigue at the neuromuscular junction or within the muscle machinery (peripheral fatigue). Then the question, first formulated in the early part of this century (2,3), arises: Do the respiratory controllers become too tired to drive the muscles to maintain adequate ventilation when the respiratory system is presented with a fatiguing load, or do the muscles become unable to generate the required force despite an adequate neural drive? These investigators, who were the first to study respiratory muscle fatigue, concluded that both types of fatigue, central and peripheral, may exist. Recently, there is increasing evidence to support the notion that about one-half of the force decline during diaphragmatic fatigue can be attributed to reduced central motor drive and the remainder to peripheral muscle contractile failure (1,4). However, it is not yet clear whether such a depression of the central nervous system (CNS) is due to primary central failure or to an adaptation of the CNS to the changes in the contracting muscle reflecting a protective mechanism to prevent an undue reduction of intrinsic muscle fiber strength.

## II. Muscle Function and Pathophysiology of Fatigue

### A. Force Generation

During a voluntary contraction a chain of events is triggered, starting with an electrical signal originating in the motor cortex and terminating with the energy-dependent interaction of actin and myosin in the muscle fiber. These events can be divided into three categories: (1) the process of delivering sufficient electrical activation from the CNS to the muscle, (2) the metabolic and enzymatic process providing energy for the contractile mechanism, and (3) the excitation-contraction coupling process that links these two.

Muscle tension at a constant length can be altered either by varying the firing frequency (rate coding or frequency coding) of each of the active motor units or by varying the number of motor units that are active (recruitment). At low

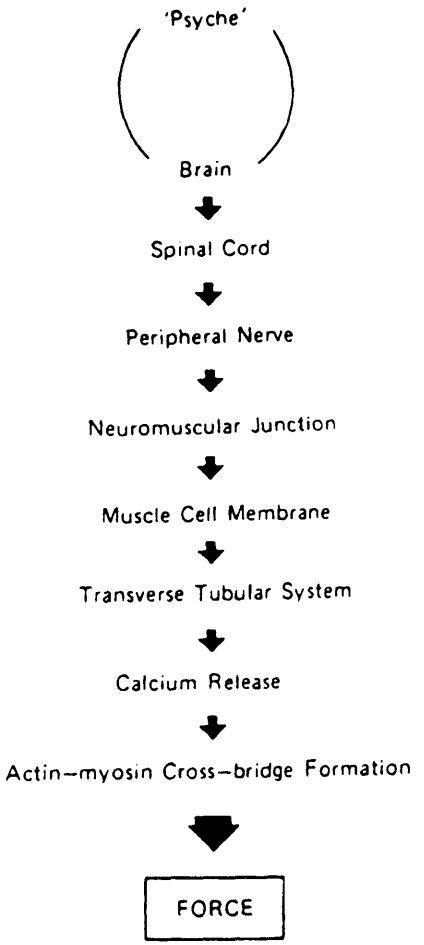


**Figure 1** Command chain for voluntary contraction of skeletal muscle. (From Ref. 12.)

intensities of muscle contraction, force is largely developed by recruitment of motor units; at moderate and high levels of voluntary contraction, the number of additional motor units recruited during a given increment in force decreases sharply and the force is generated by increasing the firing frequency of each motor unit (5,6).

Experimentally it is possible to determine the effectiveness of various firing rates in generating force (5). As the frequency increases from a single stimulus to a high-frequency train, the muscle responds with a brief twitch (unitary activity),

then an unfused (oscillatory) contraction, and finally a fused tetanus. Thus, the force-frequency characteristics of a muscle can be conveniently and effectively recorded by programmed electrical stimulation in an isolated muscle preparation (7), in human limb muscles (8,9), and in respiratory muscles (10,11) (Fig. 2). In Figure 2 it can be noted that in the pressure-frequency curve before fatigue (control), pressure increases markedly in response to small changes in low-frequency stimulation, whereas pressure is affected very little by large changes in high-frequency stimulation. The importance of the pressure (or force)-frequency curve is that central factors affecting muscle performance do not influence it. Furthermore, the manner in which it changes shape in fatigue gives insight into the mechanisms of fatigue. Selective loss of force at high stimulation frequencies (high-frequency fatigue), accompanied by a decrease in amplitude of surface-recorded action potentials, indicates fatigue of neuromuscular transmission (12) and/or impaired membrane excitation (13). Selective loss of force at low stimulation frequencies, not accompanied by a decrease in amplitude of surface action potential (low-frequency fatigue), is thought to be due to impairment of excitation-contraction coupling (8).

### B. Site and Mechanism of Fatigue

The causes of fatigue are multiple and complex and involve simultaneous changes at various sites within both the muscle and the CNS (1). Since the generation of a voluntary contraction involves the whole pathway from the brain to the muscles, the various potential sites of failure can be divided into three broad categories: (1) those that lie within the CNS (central fatigue), (2) those concerned with nerve transmission from the CNS to muscle (transmission fatigue), and (3) those within the individual muscle fibers (contractile fatigue).

Diagnosis of each type of fatigue depends on the experimental protocol by which the muscle is excited. Diagnostic features for diaphragmatic fatigue are listed in Table 1.

#### *Central Fatigue*

Central fatigue is considered present when a maximal voluntary contraction generates less force than does maximal electrical stimulation (14,15). In fact, if maximal electrical stimulation superimposed on a maximal voluntary contraction can potentiate the force generated by a muscle, a component of central fatigue is said to exist. The procedure applied for the diaphragm, first employed by Bellemare and Bigland-Ritchie (16), is the twitch occlusion test. This method examines the transdiaphragmatic pressure (Pdi) response to bilateral phrenic nerve stimulation superimposed on graded voluntary contractions of the diaphragm. It is argued that it may separate central from peripheral fatigue (1,4,16). Indeed, by using this technique the same investigators later proved that about 50% of the force decline

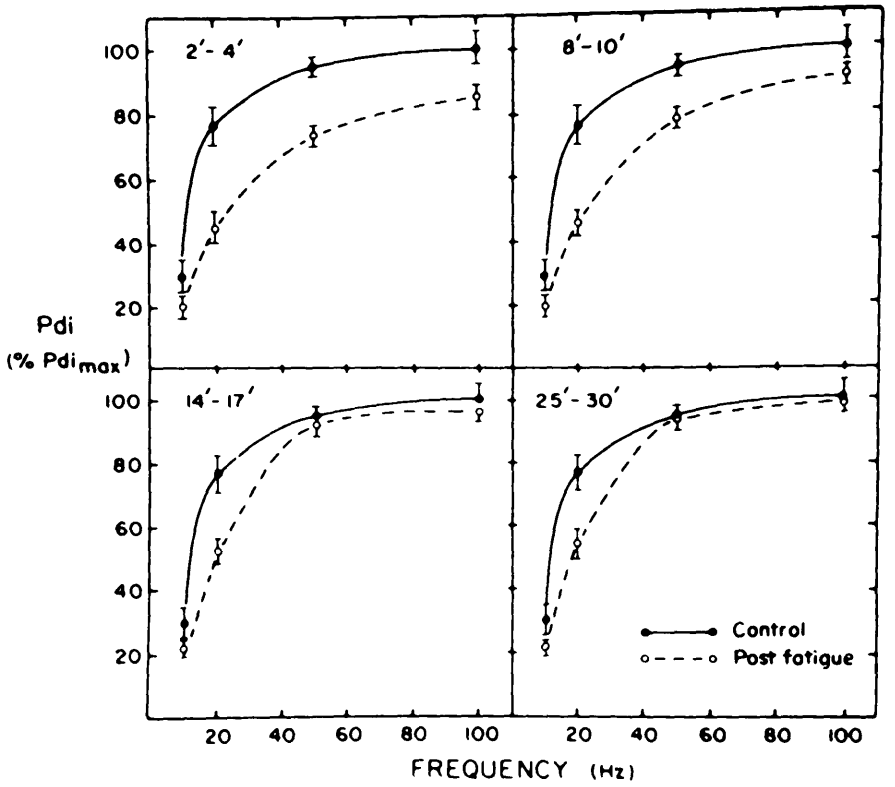


**Figure 2** Time course of changes in pressure-frequency curves of diaphragm of four subjects up to 30 minutes after fatigue. Solid curves represent average of three curves before fatigue (control); broken curves represent average of three curves at different times during recovery period; bars indicate 1SE. Transdiaphragmatic pressure (Pdi) is expressed as percent of Pdi generated with supramaximal phrenic nerve stimulation at frequency of 100 Hz (%Pdi, max). Two to 10 minutes after fatigue, the Pdi frequency curve shifts to the right so that at each frequency of stimulation, the Pdi developed is smaller than that developed before fatigue. Obviously low- and high-frequency fatigue coexist. Thirty minutes after fatigue, Pdi generated at high frequencies of stimulation (50 Hz) approaches control values, whereas low frequencies of stimulation cannot generate prefatigue Pdi values (low-frequency fatigue). (From Ref. 10.)

**Table 1** Diagnostic Features of Diaphragmatic Fatigue

| | Voluntary effort | | Phrenic nerve stimulation | | Direct muscle stimulation (animal) |
|---|---|---|---|---|---|
| | EMG response | Pdi response | EMG response | Pdi response | |
| Central | Decreased | Decreased | Normal | Normal | Normal |
| Transmission | Decreased | Decreased | Decreased | Decreased | Normal |
| Contractile | Normal | Decreased | Normal | Decreased | Decreased |

EMG = electromyogram; Pdi = transdiaphragmatic pressure.
*Source*: Ref. 149.

can be attributed to central and the other 50% to peripheral fatigue when diaphragmatic fatigue is induced by an intermittent submaximal contraction breathing protocol (4). In contrast, in some studies (14,15,17,18) during short maximal contractions central fatigue does not appear to play a role, since maximal nerve stimulation fails to increase the force. Undoubtedly, the difference between the two experimental protocols of fatigue production, i.e., intermittent submaximal contractions and short maximal contractions, may in part explain the conflicting results. However, such findings are of particular importance in understanding the pathophysiology of ventilatory failure and certainly need further testing.

Central fatigue must not be confused with progressive decrease in the firing rate during maximal contraction, during which superimposed supramaximal electric tetanic stimulation does not increase muscle force (18). Several investigators have clearly shown that the central firing rate decreases during fatiguing muscle contraction (18,20). Experimentally, the gradual loss of force following prolonged maximum voluntary contraction can be accurately mimicked with electrical stimulation if the stimulation frequency can be accurately reduced. Conversely, if high stimulation frequencies are maintained too long, force loss is more rapid. Thus, it is possible for the decrease in firing frequency to be an adaptive protecting mechanism to the alteration of muscle contractile characteristics preventing muscle exhaustion (1,18).

It is well known that fatigue is characterized not only by loss of force, but also by slowing of the muscle contractile speed. In addition, it is established that for any muscle or motor unit the minimum excitation frequency required to generate force and tetanic fusion is proportional to its contractile speed. Thus, if during fatigue the degree of contractile slowing matches the decline in motoneuron firing rate, the latter does not result in any additional reduction in muscle force. Such an adaptation would be rather beneficial. In fact, it would avoid the

failure of impulse propagation associated with high-frequency fatigue as well as the complete depletion of vital chemicals within the muscle cell, which might occur if high-frequency excitation was maintained. Of course, an interesting question is how such as adaptation is brought on. It seems likely that activation of muscle afferents by some fatigue-induced change within the muscle inhibits motoneuron activity by reducing its firing rates. In this regard, Hannerz and Grimby (21) have presented evidence that motor neurons receive a tonic inhibitory drive from peripheral sources and that during a maximum voluntary contraction the motor neuron discharge rate increases if muscle afferents are partially blocked. Such an alteration in the firing rate of the diaphragm during fatigue is not known. However, it has been shown that afferent information via large (type I and II) and small (type III and IV) fibers affects the central respiratory controller's discharge in terms of firing rate, firing time, and frequency of breathing (22); the latter is observed in states of diaphragmatic fatigue in both animal and humans (23,24). It is tempting therefore to hypothesize that, as the contractile properties and the diaphragmatic chemistry change during fatigue, chest wall or respiratory muscle afferents via the phrenic nerve may affect the output of respiratory centers in terms of firing rate or timing (frequency of breathing, duty cycle).

The strong interaction between the respiratory muscles and the CNS is well known. The interrelationship between respiratory muscle energy expenditure and its central control was first suggested by Otis (25), who concluded that for a given alveolar ventilation and mechanical properties of the respiratory system there is an optimal frequency at which minimal work is performed. Similarly, Mead (26) pointed out that the optimal frequency during spontaneous breathing is more closely associated with the minimum average force. In this regard, someone can propose that fatigue is not mainly just a failure of physiological function, but rather a protective mechanism for survival when the thorax is under excessive stress. Therefore, as speculated above, a regulatory mechanism must exist within the CNS to coordinate the motor neuron discharge to the changes in the contractile speed of the motor unit they supply and/or alteration in the muscle chemistry. An alternative hypothesis is that when fatigue ensues, the CNS alters either its firing output or its rhythmicity, which can be called "central fatigue." The work of Bellemare and Bigland-Ritchie (4) supports the fact that a central component of diaphragmatic fatigue exists. However, whether such a "central fatigue" is due to primary central failure and not to an adaptation of the CNS needs further investigation.

In summary, as fatigue ensues, the central discharge firing rate decreases and contractile slowing increases, either as primary central failure (central fatigue) or as an adaptation to the altered chemistry and/or contractile characteristics of the muscle, which may prevent their self-destruction by excessive activation. These changes in motoneuron activity are postulated to be mediated by chest wall or respiratory muscle afferents.

### *Transmission Fatigue*

During artificial stimulation of a motor neuron, especially at high frequencies, muscle force declines rapidly in association with the decline in action-potential amplitude. This response, known as "high-frequency fatigue," is attributed to failure of impulse propagation across the neuromuscular junction and/or over the muscle surface membrane. This failure may occur postsynaptically (from a decrease in end-plate excitability) or presynaptically (probably in fine-terminal filaments of the motor nerve or less frequently from depletion of synaptic transmitter substance) (27,28).

The development of this type of failure during voluntary contraction is questionable since each motor unit is excited at a rate matched to its particular contractive properties. In fact, evoked muscle compound action potential (M-wave) amplitudes are generally found to remain unimpaired, and, in addition, no unique relation between muscle force and electromyographic (EMG) activity has been observed (1). Evidence that neuromuscular transmission and cell membrane excitation are adequate during fatigue produced by voluntary contractions has been found in experiments in dogs in cardiogenic and septic shock (23,29) (Figs. 3 and 4). As the diaphragm became fatigued, the relationship of integrated phrenic nerve activity (Ephr) and diaphragmatic EMG activity remained unaltered. In other words, when the diaphragm started failing as a force generator and greater stimulation was needed for an increment of transdiaphragmatic pressure, the

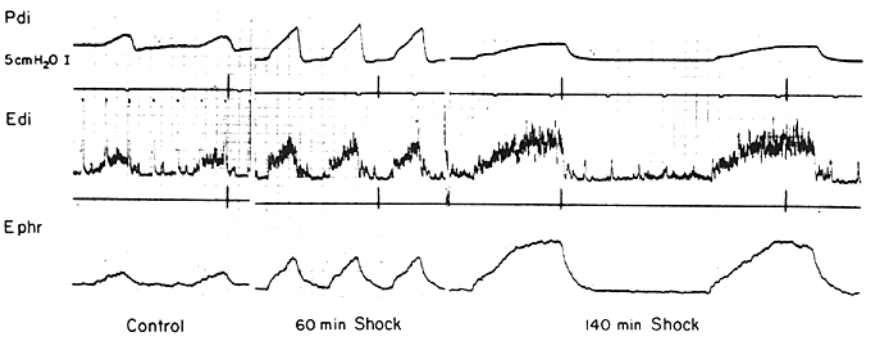


**Figure 3** Tracings from a dog in cardiogenic shock shows typical evolution of transdiaphragmatic pressure (Pdi), integrated electrical activity of the diaphragm (Edi), and integrated electrical activity of phrenic nerve (Ephr). The left panel represents a control. The middle panel shows a reading made 60 minutes after onset of cardiogenic shock. The right panel shows a reading made 140 minutes after onset of cardiogenic shock and just before the death from respiratory arrest. While Edi and Ephr continue to increase, Pdi decreases (fatigue). The decrease in size of electrocardiographic artifact on Edi trace is a consequence of injection of saline into pericardium. (From Ref. 23.)

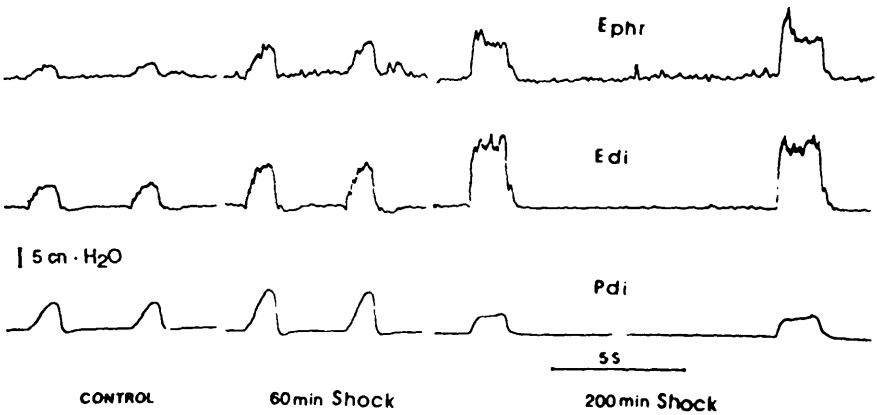


**Figure 4** Representative tracing of dog during endotoxic shock showing changes in integrated phrenic neurogram (Ephr), integrated diaphragmatic electromyogram (Edi), and transdiaphragmatic pressure (Pdi). Left, during control; middle, 60 minutes after onset of endotoxic shock; right, 200 minutes after onset of endotoxic shock and prior to death of animal. While Ephr and Edi continue to increase, Pdi decreases due to peripheral fatigue (impaired excitation-contraction coupling). (From Ref. 29.)

relationship of Ephr and EMG was similar to that observed during the control period and to the earlier stage of the fatigue (Fig. 5). However, these experiments may not be specific in testing this question; for example, changes in the wave form of action potential through the run may have compensated for discrepancies between Ephr and EMG (19). Teleologically, transmission block could be beneficial in some instances. As suggested by some authors (30–32), if failure occurs at the neuromuscular junction or in the excitation of the cell membrane, it may protect the muscle against excessive depletion of its ATP stores, which would lead to rigor mortis. If high-frequency fatigue is due to failure of the neuromuscular junction, it may be speculated that such a failure can exist in the diaphragm of humans. In fact, it has been clearly shown that normal subjects breathing against inspiratory loads develop high-frequency fatigue (10) (Fig. 2), which may reflect neuromuscular junction failure.

### *Contractile Fatigue*

Most studies conclude that the major factors underlying neuromuscular fatigue occur within the muscle fibers and result mainly from depletion of muscle energy stores or pH changes from lactic acid accumulation (1). The substances directly involved in the transformation of chemical energy into mechanical work in skeletal muscles are ATP, ADP, inorganic phosphate (Pi), hydrogen ions ($H^+$),

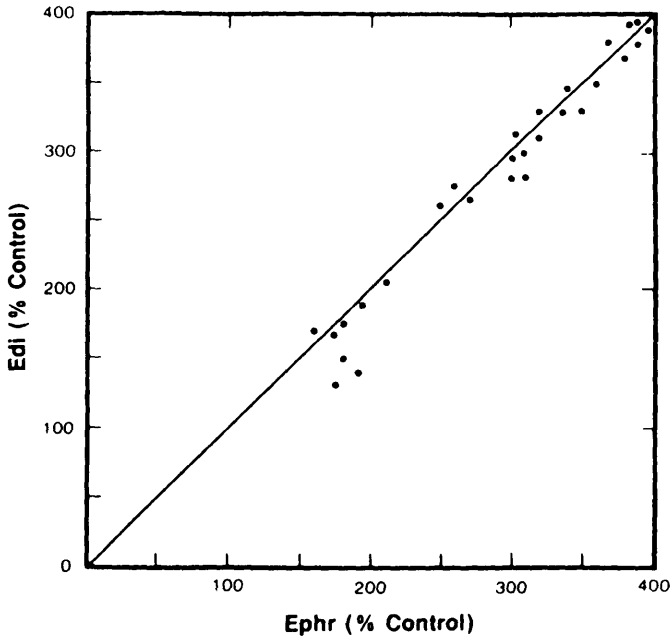


**Figure 5** Relationship between individual changes in electrical integrated activity of phrenic nerve (Ephr) and diaphragm (Edi) during fatigue developed by endotoxic shock for three dogs. Changes are expressed as percentage of control values. Ephr and Edi are well correlated ($r = 0.951$). These data suggest lack of failure of impulse propagation across the neuromuscular junction and/or over the muscle surface membrane. (From Ref. 29.)

magnesium ions ($Mg^{2+}$), and phosphocreatine (Pc). ATP leaves the mitochondria and diffuses in the contractile machinery of the cell, where ATPase enzymes hydrolyze one of the pyrophosphate bonds, liberating large quantities of energy in the process:

$$MgATP + H_2O \xrightarrow[ATPases]{} MgADP + Pi + H^+ + \text{energy}$$

High levels of exercise or hypoxia result in the accumulation of ADP, Pi, and lactate, as well as decreases in Pc and pH. The decrease in Pc and the concomitant increase in Pi provide a convenient index of cellular energy state, the Pc:Pi ratio (33). In the past, measures of this ratio could be obtained only by destructive tissue biopsy procedures. This has been changed with the introduction of 31-phosphorus magnetic resonance spectroscopy ($^{31}$P-MRS), a technique that makes it possible to sequentially monitor changes in Pc, Pi, and ATP in the muscle during hypoxia, exercise, or fatigue in an accurate and noninvasive manner (33). Using this

technique, Dawson et al. (34) showed that during fatigue Pc breaks down progressively and creatine, ADP, and $H^+$ levels rise while ATP, the direct source of energy, is reduced only 25%. The latter finding is consistent with the results obtained in normal subjects performing dynamic exercise until exhaustion (35). They found that at high work loads, when Pc was practically depleted, ATP decreased to 40% of its control value. Why, then, does the muscle become unable to generate force in the presence of adequate sources of ATP? To answer this, we must consider the above-mentioned hydrolysis of ATP. As the muscles fatigue, the concentration of all byproducts increases considerably and therefore this reaction is delayed. This leads to the hypothesis, so far untested in the diaphragm, that the decline in muscle force is not due to the depletion of ATP but to the reduced rate of ATP breakdown because of product accumulation.

The increase in energy demands in the working skeletal muscles, including the respiratory muscles, is provided mainly by the combustion of fat, blood glycose, and glycogen of the muscle. During submaximal prolonged heavy exercise, exhaustion coincides with the depletion of muscle glycogen, whereas exercise capacity is enhanced when the storage of muscle glycogen is increased (36). Similar observations have been made in the diaphragm of dogs with low cardiac output (37). However, why glycogen depletion coincides with fatigue is not clear. During prolonged intermittent heavy exercise that depends on aerobic metabolism, the rate of utilization of fatty acids and glycose is high; although these substances circulate in large amounts in the bloodstream, they cannot provide sufficient energy to the muscle to meet the demands. Hence, muscle glycogen must be used to supplement the bloodborne fuels and fatigue will occur when it is depleted.

A great deal of attention has been focused on the role that lactic acid plays in the development of fatigue. This is the result of a firm correlation that exists between lactic acid accumulation in the muscle and contractile force (34,38). Similarly, blood lactate elevation has been found in subjects breathing through high inspiratory loads to exhaustion (39), but there is no direct evidence that the lactic acid produced by the respiratory muscles is the culprit in diaphragmatic fatigue. Furthermore, animals in cardiogenic shock develop substantially less lactic acidosis if they are mechanically ventilated than if they are breathing spontaneously (37), indicating that the respiratory muscles produce great amounts of lactic acid if they are working under fatiguing conditions.

The effects of lactic acid on force generation are believed to be mediated by lowering the pH, which is a well-established reason for decrease in skeletal muscle force. At low pH, $Ca^{2+}$ is sequestered in the sarcoplasmic reticulum (40) and a larger amount of $Ca^{2+}$ is needed to produce a given tension with this low pH. In addition, hydrogen ions exert a direct negative effect on the contractile process itself (42).

Recently, lactic acid accumulation (and pH fall) in the respiratory muscles

has been linked to the reduction in central respiratory output secondary to increased endogenous opioid activity during inspiratory flow-resistive loading (43) (Fig. 6). Increased respiratory muscle lactic acid is considered to be a strong stimulant of afferent fibers (Group III and IV), which can signal the release of endogenous opioids.

Metzger and Fitts (44), using glass microelectrodes, found decreases in intracellular pH from 7.03 to 6.33 with stimulation in a rat diaphragm preparation as it developed high- and low-frequency fatigue. They concluded that intracellular acidosis was associated with muscle fatigue, probably produced by the inhibition of phosphofructokinase, a key enzyme in the control of glycolysis. However, to date, it is not entirely clear if intracellular acidosis is the cause or a manifestation of diaphragmatic fatigue (33). It seems that intracellular acidosis may have a more important effect during the recovery period than during active contraction (45). It also appears that extracellular acidosis plays a key role during recovery from fatigue (46) since lactate efflux from cells ceases when the extracellular pH falls to 6.8. Furthermore, Fitzgerald et al. (47), using $^{31}$P-MRS to study the effects of metabolic and compensated metabolic acidosis on an in vitro rat diaphragm

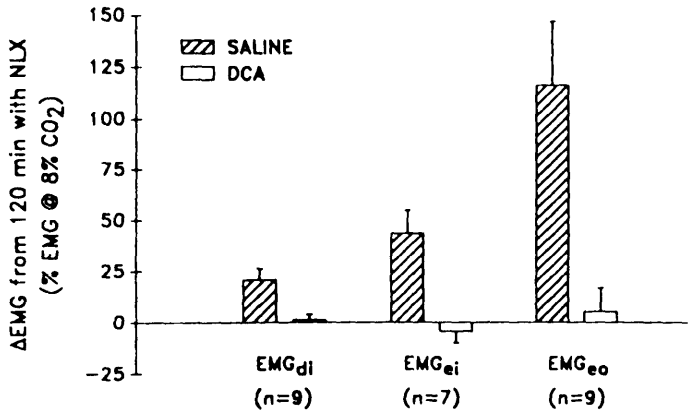


**Figure 6** Respiratory muscle EMG responses to naloxone (NLX) after 120 minutes of exposure to saline or DCA (open bars = DCA; hatched bars = saline; * = $p<0.05$ vs. EMGdi). During 2 hours of inspiratory loading (50 $cmH_2O/L/sec$), goats were exposed to a constant infusion of either saline or dichloroacetate (DCA), a compound that enhances the activity of pyruvate dehydrogenase and thus lessens the production of lactic acid. NLX (0.3 mg/kg) was given at the conclusion of the loading period. In the goats given saline, NLX significantly increased EMG of the diaphragm (EMG di), external oblique ($EMG_{eo}$), and external intercostal ($EMG_{ei}$). DCA infusion completely blocked the NLX effect on respiratory activity, suggesting that lactic acid is the stimulus signaling the activation of the endogenous opioid system. (From Ref. 43.)

preparation, proved that the decrease in diaphragmatic force during acidosis is not the result of a loss of high-energy phosphates, Pi, or ATP, but the consequence of acidosis per se.

To summarize, glycogen depletion, lactic acid accumulation, acidosis of every kind, inability to utilize bloodborne substances, decrease in the rate of ATP hydrolysis, and reduction in central respiratory output by lactic acid through an increase in endogenous opioid activity are merged to explain loss of force. However, the exact interplay of all these factors is not yet identified in either the diaphragm or the other skeletal muscles.

#### *Impaired Excitation-Contraction Coupling*

All processes that link the electrical activation of the muscle fiber and the various metabolic and enzymatic processes providing energy to the contractile machinery are called excitation-contraction coupling processes. Impaired excitation-contraction coupling is thought to be involved when the loss of force is not accompanied by a parallel decline in the electrical activity (15). This type of fatigue is characterized by a selective loss of force at low frequencies of stimulation (low-frequency fatigue) despite maintenance of the force generated by high frequencies of stimulation, indicating that the contractile proteins continue to generate force (Fig. 2). This type of fatigue is not related to depletion of ATP or phosphocreatine (Pc) and is characteristically long-lasting, taking several hours to recover. The mechanism of this type of fatigue is not well known. It may occur because of a reduced supply of $Ca^{2+}$ or a change in the affinity of the troponin binding site for $Ca^{2+}$. These defects would reduce the twitch and hence would reduce the force developed at low stimulation. In contrast, at higher stimulation frequencies, a relatively normal force can be generated when the interior of the fiber is saturated with $Ca^{2+}$ (9,48). Other possibilities include structural damage (49) or an alteration in the compliance of the series-elastic component of the muscle (50).

Impaired excitation-contraction coupling occurs in the diaphragm of the dog during cardiogenic or septic shock (23,29); despite a threefold increase of the integrated EMG, Pdi decreased (Figs. 3 and 4). In addition, low-frequency fatigue and by inference impaired excitation-contraction coupling has been found in the diaphragm and sternomastoid of normal subjects after they breathed against very high inspiratory resistance (10,11).

### C. The Role of Endogenous Opioids and Thin Fiber Afferents in the Reduction of Central Motor Output

Since the respiratory depressant effects of opiate drugs such as morphine and meperidine had been well described (51–53), the discovery of endogenous opioid receptors and ligands in the CNS led to speculation that these peptides might also

be involved in ventilatory control (54). An early study by Santiago and coworkers (55) demonstrated that the opioid antagonist naloxone could restore the flow-resistive load compensation reflex in those patients with chronic obstructive pulmonary disease in whom it was initially absent. They postulated that in these patients endogenous opioids were elaborated in response to the stress of a chronically increased airway resistance and that this resulted in attenuation of the respiratory compensation for the increased airway resistance, perhaps as a mechanism by which the sense of dyspnea might be reduced. However, this finding was not confirmed in a subsequent controlled study by Simon et al. (56).

In an animal model Scardella et al. (57) demonstrated that relatively short-term but high-intensity flow-resistive loading could be sufficient to activate the endogenous opioid system and modify the subsequent respiratory response. They found a progressive reduction in tidal volume in the course of resistive loading in unanesthetized goats. This was partially reversed by administration of naloxone (Fig. 7). These authors also demonstrated an increase in beta-endorphin immunoreactivity in the cisternal cerebrospinal fluid (Fig. 8). From the same laboratory, Edelman and colleagues showed the role of activation of the endogenous opioid system in selective inhibition of the abdominal muscles, compared to the diaphragm (58,59). Their findings suggested that the intense activity of the respiratory muscles, especially the abdominal muscles, serves as a "noxious" stimulus resulting in activation of the endogenous opioid system. Reduction of central respiratory output appeared to occur to a greater extent in the muscles receiving the greater stimulus. This pattern of endogenous opioid-mediated depression was similar to that which occurs in the antinociceptive pain control system, where it has been demonstrated that endogenous opioid-medicated analgesia is specific to both the peripheral noxious stimulus and the region receiving the stimulus (58,59). The specificity of the attenuation of a respiratory muscle activity by endogenous opioids is related to the degree of lactic acid accumulation in the muscle (60). Two lines of evidence support this concept. First, dichloroacetate blocks the naloxone-mediated increase in respiratory muscle activity during loading, and second, the decrease in interstitial pH during loading is greater in the external oblique abdominal muscle than the diaphragm (43). Furthermore, other work by the same investigators (60) raises the possibility that part of the reduction in centroid frequency associated with diaphragmatic fatigue may result from reductions in central respiratory output associated with elaboration of endogenous opioids. They examined the changes in the power spectrum of diaphragmatic EMG during loading and naloxone infusion (Fig. 9) and postulated that a reduction of overall motor unit activation is likely to be biased towards inactivation of high-frequency units as reflected in the high-frequency power content of diaphragmatic EMG power spectrum, thereby reducing centroid frequency.

Although the above results indicate that in animals endogenous opioid pathways are activated in response to the acute increase in airway resistance

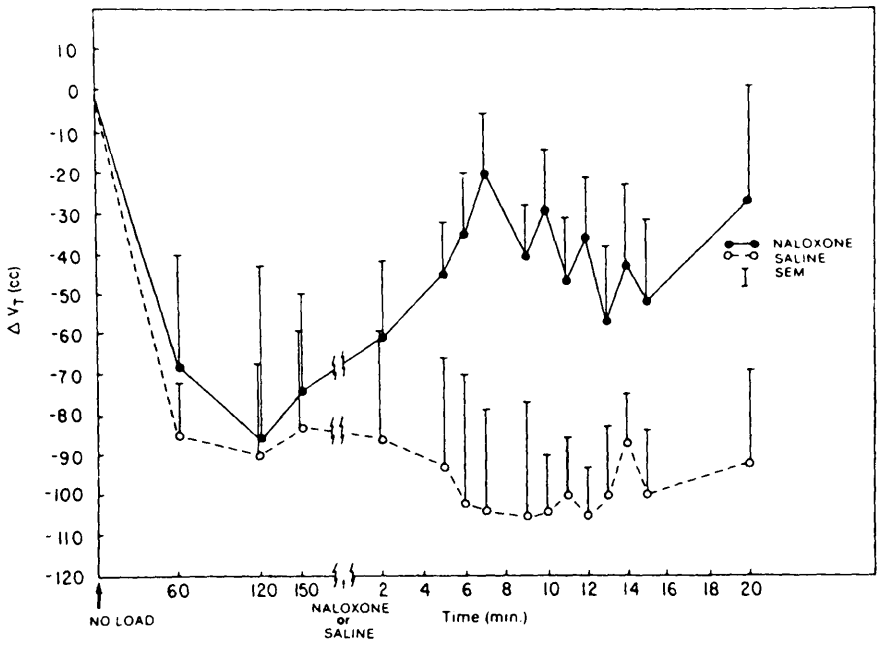


**Figure 7** Tidal volume response of unanesthetized goats to 2.5 hours of high inspiratory flow resistive loading prior to and following the administration of naloxone. Tidal volume, which fell considerably during loading, increased significantly but transiently after naloxone administration, while saline had no effect. (Note the change in time scale on the x-axis.) These data indicate that an increase in airway resistance can activate the endogenous opioid system. Furthermore, the increase in tidal volume immediately following naloxone suggests that these potentially fatiguing loads reduce tidal volume prior to the onset of overt muscle fatigue by a mechanism that, in addition, to the direct mechanical effect of the load, involves the endogenous opioid system. (From Ref. 57.)

reducing overall ventilatory output, in humans the role of endorphins in central fatigue has not been adequately evaluated and remains uncertain. One possible example of endogenous opioid activation in the face of an increased respiratory load in humans was recently described (61). In asthmatics with methacholine-induced severe reductions in forced expiratory volume in 1 second ($FEV_1$), naloxone pretreatment resulted in increased breathing frequency, occlusion pressure, and mean inspiratory flow rate when compared to saline pretreatment.

The effect of phrenic afferents on central controllers has been investigated recently by many groups with particular focus on the effect that small fibers (types III and IV) exert on the timing of breathing and the sensorimotor cortex (21,22,62,63). Despite some difference among authors, all agree that the supraspi-

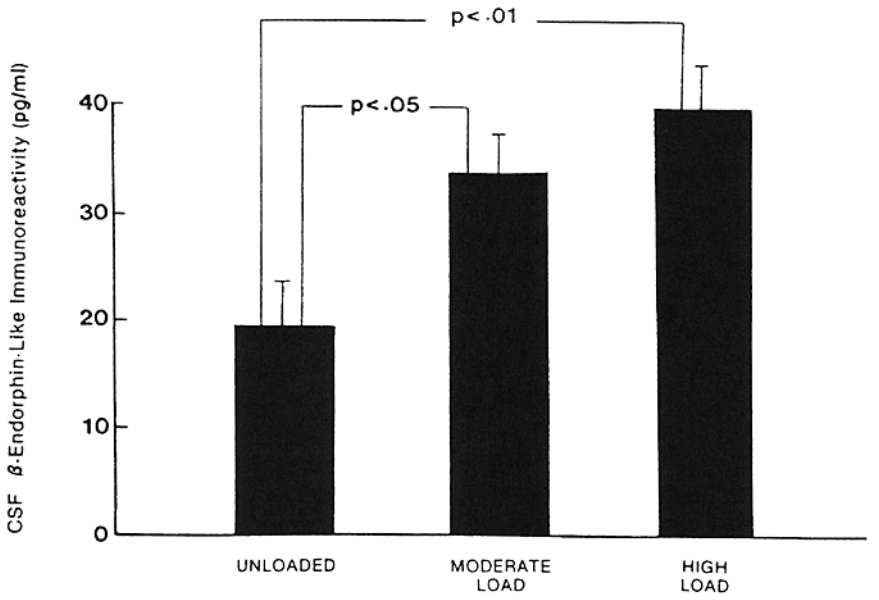


**Figure 8** Beta-endorphin–like immunoreactivity in cisternal cerebrospinal fluid (CSF) in unanesthetized goats in control (unloaded) and under two loading conditions. Beta-endorphin immunoreactivity was significantly increased with the moderate ($p < 0.05$) and high ($p < 0.01$) loads when compared to the unloaded state. (From Ref. 57.)

nal projections of those afferents have an effect on the control of breathing. These sensory fibers are activated primarily by extracellular metabolic changes (e.g., low pH, ischemia, increased osmolarity), and some substances (phenyldiguanide, capsaicin). Recently, Petrozzino et al. (43) demonstrated that the reduction in central respiratory output secondary to increased endorphin activity is signaled by small fiber afferents, which are stimulated by lactic acid accumulation and pH fall in the respiratory muscles. Thus, it is possible that afferents via the small fibers during loaded breathing in various clinical states modulate endogenous opioids as an adaptive response—much the same as opioids are generated in response to chronic pain. This strategy certainly minimizes breathlessness and may avoid or delay the onset of respiratory muscle fatigue, protecting the ventilatory pump from exhaustion, which undoubtedly is a very terminal event.

### D. Integrated View of Respiratory Muscle Fatigue

Fatigue is likely to be the result of a dynamic process in which compensatory mechanisms are overwhelmed in a closed-loop system consisting of central motor

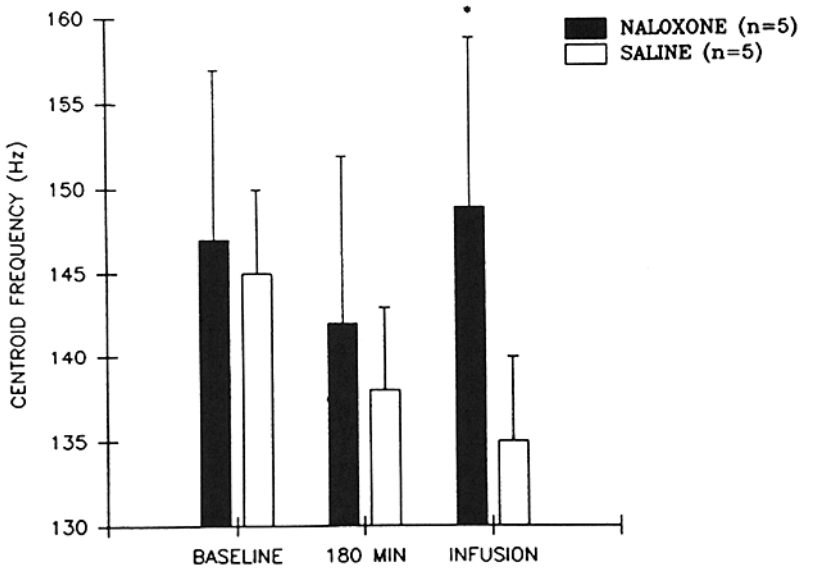


**Figure 9** Centroid frequency at baseline, 180 of loading, and after infusion of naloxone or saline. During 180 minutes of inspiratory loading (50 $cmH_2O$)/L/sec), diaphragmatic EMG (EMGdi) was recorded. Centroid frequency of the EMGdi power spectrum decreased significantly by 180 minutes of loading. Naloxone completely reversed the decrease in centroid frequency, while saline administration had no effect ($*p < 0.05$ vs. 180 min). (From Ref. 60.)

drive, peripheral impulse propagation, excitation/contraction coupling, depletion of energy substrates, and/or metabolite accumulation and feedback–modulating reflexes (1). The site of fatigue may be placed at any level from the CNS to the contractile machinery depending on the experimental setting. For an individual muscle there exists a close relationship between excitation and energy metabolism (34). It has been shown that a protective mechanism may exist at the site of the action potential or beyond, so that when there is a depletion of fuel, failure of the activation system occurs and in extreme fatigue prevents the muscle from destroying itself, which would happen if the ATP level fell to zero. A decrease in excitation may result from failure of the neuromuscular junction (27,30–32), or it may stem from a reduced rate of firing by the CNS (20), or both. In the respiratory system, in addition to the reduction in firing frequency, the CNS may respond by altering the frequency and the duty cycle (23). Although it has not yet been proved, such an alteration in the responses of central controllers could be brought about by afferents from the fatiguing inspiratory muscles and the chest wall. During fatigue the normal inhibitory influence from Golgi tendon organs pre-

sumably declines with the loss of force, but concomitant fatigue of intrafusal fibers might reduce the excitatory response of muscle spindles. Furthermore, free nerve endings within the muscle might inhibit motoneuron activity in response to muscle stretch and fatigue. Afferent information via small (types III and IV) fibers possibly reduce central respiratory output by modulating endorphins as an adaptive response to avoid or delay respiratory muscle fatigue.

## III. Determinants of Critical Task

The threshold of fatigue is that level of exercise and/or mechanical loading that cannot be sustained indefinitely. This level can be expressed as a percentage of maximum performance. Monod and Scherrer (64) used this approach for intermittent contractions to determine the critical force above which fatigue ensues. The authors also suggest that fatigue will develop when the mean rate of energy demand ($\dot{U}d$) exceeds the mean rate of energy supply ($\dot{U}s$).

$$\dot{U}d > \dot{U}s \tag{1}$$

Thus

$$\dot{W}/E > \dot{U}s$$

or

$$\dot{W} > \dot{U}sE \tag{2}$$

where $\dot{W}$ is mean muscle power and E is efficiency. Clearly when $\dot{U}sE \geq \dot{W}$, the muscle can continue to work indefinitely, but when $\dot{U}sE < \dot{W}$, there will be a finite endurance time. Thus, a decrease in either efficiency or energy supplies should predispose to fatigue, as would an increase in muscle power. Although exhaustion of energy supplies does not account for failure of force development, fatigue (like angina pectoris) can be analyzed in terms of the balance between energy supply and demand. For the inspiratory muscles during inspiratory resistive breathing with the mouth pressure developed in a square-wave manner, the endurance time becomes infinite when $\dot{W}$ = 6–8 kg/min, effectively preventing muscle fatigue (65). This implies that $\dot{U}sE$ is also 6–8 kg/min; these values are called critical power and rate of energy supply, respectively.

If the pressure generated by the inspiratory muscles assumes a square waveform, the term $\dot{W}$ becomes

$$\dot{W} = PV_Tf = PV_T(1/T_T) \tag{3}$$

where P is mean inspiratory pressure and f is frequency of breathing. $V_Tf$ or $V_T$ $(1/T_T)$ equals minute ventilation. Multiplying numerator and denominator by $T_I$, Eq. (3) becomes

$$\dot{W} = P(V_T/T_I)(T_I/T_T) \quad (4)$$

where the product of $V_T/T_I$ and $T_I/T_T$ denotes minute ventilation. As a first approximation, $T_I/T_T$ expresses the proportion of duration of inspiratory muscle contraction to the total duration of the breathing cycle. Substituting Eq. (4) into Eq. (inequality) (2) yields

$$P(V_T/T_I)(T_I/T_T) > \dot{U}sE \quad (5)$$

Clearly the power of the respiratory muscles can be greater than, equal to, or smaller than the available energy in a variety of combinations of P, $V_T/T_I$, and $T_I/T_T$. Thus, Roussos et al. (65) found that the critical pressure of all the inspiratory muscles is 50–70% of the maximum, and for the diaphragm alone it is 40% of the maximum for a $V_T/T_I$ of 0.6–0.9 L/sec and a $T_I/T_T$ of 0.3–0.4. Furthermore, in keeping with the predictions of inequality (5), Bellemare and Grassino (66) found that the critical Pdi decreases as the $T_I/T_T$ increases at a constant $V_T/T_I$. They found that when the product $(Pdi/Pdi_{max})$ $(T_I/T_T)$ exceeds 0.15, there is a finite endurance time.

One would predict that if ÚsE decreases (either decreasing the energy supply or efficiency or both), the critical values of pressure or the combination of pressure, flow, and duty cycle will change. For example, reduction in Ús by reducing cardiac output in dogs results readily in diaphragmatic fatigue (23) (Fig. 3). Similarly, altering the efficiency, as might occur in resistive breathing compared to unobstructed hyperventilation, may substantially alter critical pressure or power. In fact, Tenney and Reese (67) found that the critical power ($\dot{W}$crit) during hyperventilation is at least four times greater, corresponding to 55% of maximum breathing capacity (Fig. 10), than the $\dot{W}$crit (and ÚsE) of 6–8 kg/min found during resistive breathing in normal subjects (65). Similar arguments may account for the smaller critical Pdi if the diaphragm operates at shorter lengths during acute hyperinflation, when a given force requires much greater excitation (68).

In summary, there is clear evidence of a critical force that, if exceeded, results in fatigue. This critical force, however, is largely affected by many factors—for example, the total duration of contraction per breath (pressure-time index), velocity of contraction, operational length, energy supply, efficiency of the muscles, and state of muscle training.

## IV. Diagnosis of Inspiratory Muscle Fatigue

It is obvious in the definition of fatigue that its detection requires techniques that estimate force, particularly if these relate to the degree of muscle excitation. More specifically the force should be related to the intensity and frequency of stimulation, the fiber length, and the velocity of shortening. If this is achieved, contractility can be estimated. The bedside clinical diagnosis of fatigue, however, is

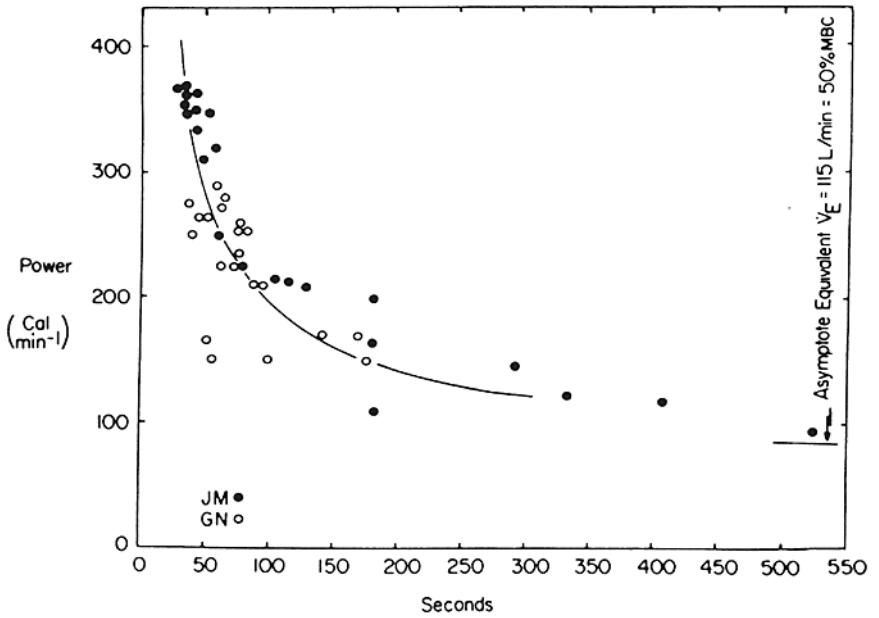


**Figure 10** Power of breathing traced as a fraction of endurance time for two subjects. Curve is asymptotic at a power that would permit ventilation ($\dot{V}_E$) of about 50% maximum breathing capacity (MBC). (Adapted from Ref. 67.)

hampered by the inability to measure the baseline before fatigue (1). It may be possible only to infer fatigue retrospectively by its reversibility after a period of rest. Currently, there are the following tests to detect respiratory muscle fatigue:

1. Tests that measure the pressures generated by the respiratory muscles [maximal inspiratory mouth ($P_I$max) or transdiaphragmatic pressure ($Pdi_{max}$) and the pressure generated per breath (Ptidal) divided by the maximal (Ptidal/$Pdi_{max}$) and with respect to inspiratory time and respiratory rate (pressure-time index)]
2. Tests that measure diaphragmatic or other inspiratory muscle electrical activity [power spectral analysis and integrated electrical activity (Edi) or some combination of electrical activity and pressure development (Edi/Pdi)]
3. Tests that aim to assess the capacity of the diaphragm to generate pressure independent of central control mechanisms [bilateral phrenic nerve twitch stimulation and pressure-frequency (Pdi/frequency) curves]

4. Tests that measure the increase in Pdi when a twitch is superimposed on the naturally activated diaphragm to detect the relative degree of motor unit recruitment through central pathways (twitch occlusion test)

Each of these tests has its own limitations. For example, when interpreting $P_I max$ and $Pdi_{max}$, submaximal efforts cannot be distinguished from central fatigue. Tests that quantitate the electrical activity of inspiratory muscles are influenced by changes in the relationships between the recording electrodes and the muscle.

The measurement of force-frequency curves is a useful and specific technique for detecting peripheral fatigue. Measurement of the force-frequency curve of the diaphragm is made possible by stimulating the phrenic nerve and recording transdiaphragmatic pressure (69,70). The curve can easily be documented for the sternomastoid muscle by stimulation of the muscle with surface electrodes (11). Loss of force at low-frequency stimulation indicates impairment of excitation contraction coupling (Fig. 2). Loss of force at high-frequency stimulation indicates impairment of the neuromuscular junction or of membrane excitation. There are, however, several sources of error in the use of such curves. It is not possible to supramaximally stimulate the phrenic nerve transcutaneously. Thus, when comparing curves, it is important to be certain that the nerve receives exactly the same stimulation. Furthermore, the contraction must be isometric or the degree and velocity of shortening as well as the initial fiber length and geometry of the diaphragm must be identical. Provided these variables are properly controlled, the change in the force-frequency curve gives information about the underlying mechanism of the peripheral fatigue, as previously mentioned. When one cannot be certain that the nerve receives the same stimulation, curves measured at different times can still be usefully analyzed by comparing the ratio of pressure developed at a given frequency with that obtained at 100 Hz; this gives information on the shape of the curve. The ratio is high in high-frequency fatigue and low in low-frequency fatigue (71).

The force developed for a given degree of excitation can also be estimated by relating Pdi to the integrated electrical activity of the diaphragm (Edi) during a Müller maneuver against a closed airway. A reduction in the Pdi:Edi ratio at constant length and geometry is a good index of peripheral muscle fatigue (impaired excitation-contraction coupling). Care must be taken to ensure that the contraction is isometric (i.e., no displacement of either rib cage or abdomen) and that electrode placement and electrical impedance are identical. The Pdi:Edi ratio can also be used during spontaneous breathing (Figs. 3 and 4).

As fatigue develops, the time that a muscle takes to relax is known to be prolonged. The assessment of decay of the relaxation rate of the diaphragm during fatigue has been found to correlate significantly with the rate of decay of H/L (EMG) (72). The test can be performed easily and noninvasively by using sniffs as a means of generating maximal voluntary diaphragmatic contractions (73).

### A. Twitch Occlusion Test

This is the only test among those used to detect respiratory muscle fatigue that can separate central from peripheral fatigue. This method was originally introduced by Merton (15). However, the ones who expanded its use, extracting very important data, were Bellemare and Bigland-Ritchie (4,16). They employed the method of twitch occlusion to test whether, following repetitive contractions of the diaphragm in normal human subjects to the limits of its endurance, the nervous system would be able to fully activate the diaphragm in response to a command for maximal voluntary effort (16). This method examines the Pdi response to bilateral phrenic nerve stimulation superimposed on graded voluntary contractions of the diaphragm. The amplitude of Pdi twitches in response to phrenic nerve stimulation decreases as the voluntary Pdi increases. During maximal voluntary contractions of the diaphragm ($Pdi_{max}$), no superimposed twitches are detected (Fig. 11). In a later study (4), the same authors inducted diaphragmatic fatigue, loading the diaphragm by either resistive loads or expulsive contractions against a bounded abdominal wall, and administered single bilateral phrenic shocks during (Ts) and between (Tr) contractions. Single shocks were also administered during voluntary

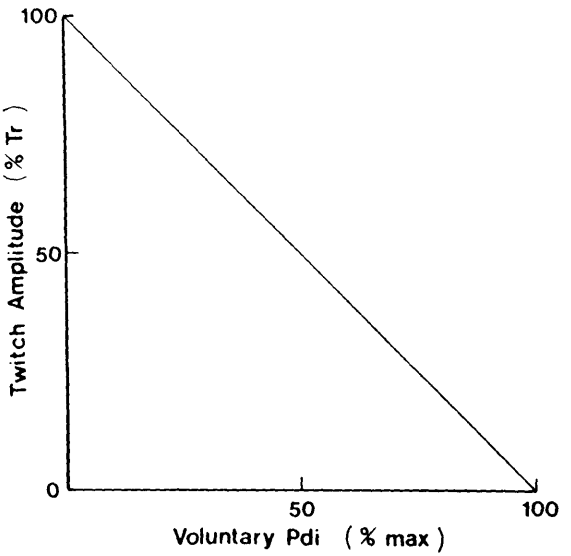


**Figure 11** The relationship between voluntary $Pdi_{max}$ and superimposed twitch amplitude (expressed as a percent of the twitch amplitude of the relaxed diaphragm, Tr). As voluntary $Pdi_{max}$ increases, the magnitude of the superimposed twitch decreases. (Adapted from Ref. 4.)

$Pdi_{max}$ contractions. At the start of the experiment they found that central respiratory drive was able to fully activate the diaphragm since no superimposed twitches could be detected during $Pdi_{max}$ contractions, a finding consistent with their previous study (16). During the course of loaded breathing, the degree to which full muscle activation could be achieved decreased, as evidenced by the finding that superimposed twitches could be demonstrated at the limits of diaphragmatic endurance. At these limits, voluntary $Pdi_{max}$ had decreased by 50%, whereas the $Pdi_{max}$ estimated from the twitch occlusion had decreased by only 25% (Fig. 12). This study showed that at the limits of diaphragmatic endurance, even though peripheral fatigue was present, a significant portion of the reduction in the force was due to failure of the CNS to completely activate the diaphragm.

This test has been enthusiastically endorsed by the NHLBI workshop (1). It was recommended that this test be evaluated and compared with others in order to determine the value and utility of each and thus describe their specificity and sensitivity. This technique is particularly appropriate for clinical studies since it is relatively painless, easy to apply, and can be used on muscles where motor nerve is not readily accessible. Moreover, maximal muscle strength can be indirectly and accurately assessed under conditions where the patient is unable or unwilling to make a truly maximal effort.

One drawback when using this technique to investigate fatigue of the diaphragm is that consistent supramaximal bilateral tetanic stimulation of the phrenic nerves has so far proved unreliable (1). Thus, changes in intrinsic muscle strength can so far only be assessed from changes in the twitch responses elicited from the relaxed muscle. These responses may be subject to fluctuations, e.g., substantial degrees of twitch potentiation or "low-frequency fatigue," not seen when tetanic stimulation is applied. Despite these drawbacks, it is felt that information obtained from bilateral transcutaneous supramaximal phrenic nerve twitch stimulation has the best potential of becoming a diagnostic test of respiratory muscle fatigue (1). Recently, in order to minimize the invasivity of the balloon-catheter technique to measure twitch transdiaphragmatic pressure, which limits its clinical use, the measurement of mouth pressure twitch against an occluded airway has been developed (74). Although it can potentially be used as a twitch occlusion test, more rigorous evaluation needs to be done before it can be recommended for general use (1).

### B. EMG Spectral Shift

Analysis of the EMG in its frequency part delineates its power spectrum; with fatigue this spectrum shifts to lower frequencies. This approach has been used for many years in other skeletal muscles (75) and during the last decade in the respiratory muscle (76); however, the underlying cellular mechanisms remain unknown. Among the theories that attempt to explain this shift, the most popular

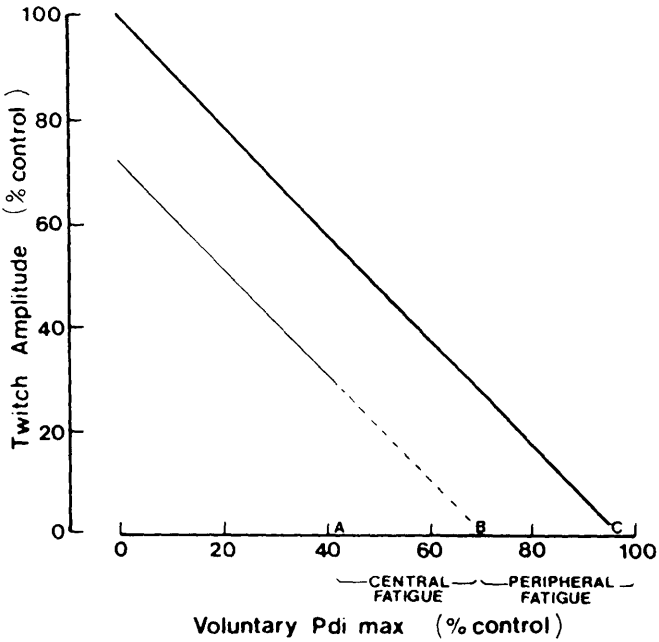


**Figure 12** The relationship between the voluntary Pdi and superimposed twitch amplitude during control experiments performed prior to loading (upper line) and during loading after the limits of endurance had been reached (lower line). The difference between the point where the lower line intersects the x-axis (predicted voluntary $Pdi_{max}$ if the diaphragm was fully activated (point B) and the actual maximal voluntary Pdi (point A) represents the contribution of the lack of central drive (central fatigue) in generating $Pdi_{max}$ (the difference between points A and B). The difference between the point where the upper line interacts the x-axis, which is the unfatigued $Pdi_{max}$ (point C), and the point where the lower line intersects the x-axis (point B) represents the contribution of peripheral muscle fatigue to the generation of $Pdi_{max}$ (the difference between points B and C). (Adapted from Ref. 4.)

remains the slowing of conduction velocity (77); the spectral shift observed during fatigue could be explained by a progressive slowing of conduction velocity, which would in turn prolong the fiber action-potential wave form. Mortimer et al. (78) suggested that slowing of conduction velocity may result from the accumulation of metabolites, such as lactic acid. The accumulation of lactate is unlikely in itself to explain the EMG changes because patients with myophosphorylase deficiency who do not produce lactic acid have the same change in the EMG power spectrum during fatigue (79). However, the findings of other authors (80,81) indicate that there is no relation between conduction velocity and changes in the power spec-

trum during both fatiguing and nonfatiguing muscle contractions. They concluded that factors other than changes in the waveform of individual muscle fiber action potentials must contribute to the observed shift in the total EMG frequency components.

The relationship between the power-spectral shift and fatigue is empirical. It occurs in the diaphragm before there is failure to develop adequate force and thus is a useful objective measure to predict and precede the onset of fatigue (Fig. 13). With the new definition of respiratory muscle fatigue (1), which depicts that fatigue may be present at a time considerably preceding the point in time at which a muscle is unable to continue to perform a particular task, it is possible that the power spectral shift tracks the development of fatigue with considerable accuracy (82). However, a single measurement of the power spectrum is insufficient and a change must be observed in order to predict fatigue. In addition to the fact that the electrical activity of inspiratory muscles is influenced by changes in the spatial relationships between the recording electrodes and the muscle, power spectrum changes can result from conditions other than muscle fatigue. Thus, doubt is cast upon the sensitivity and specificity of this technique (1).

Further work is needed to elucidate the pathogenesis of the changes in the EMG power spectrum (71). Such studies should help us understand the mechanism and site of fatigue. What is clear so far is that one cannot equate electromyographic indices of fatigue to contractile fatigue. Under certain experimental conditions, changes in the EMG power spectrum are associated with high-frequency fatigue, whereas the EMG power spectrum is normal in low-frequency fatigue (83). Thus, the power-spectral shift might signal fatigue due to reduced central firing frequency, neuromuscular junction failure, failure in the excitation of sarcolemma, or failure in the synchronization that occurs during fatigue, but it may be insensitive to failure in excitation-contraction coupling or in the contractile machinery (71).

### C. Clinical Detection of Fatigue

An interesting and important feature of the fatiguing inspiratory muscles is the alternation in the contribution of each group of muscles (diaphragm or intercostal/accessory) to the breathing task (24,65,84). When a normal subject breathes against a fatiguing load, during which he attempts to maintain a constant mouth pressure, three stages of breathing from the point of view of breathing pattern and ability to maintain the required task have been observed (Fig. 14). At the beginning, the timing of breathing and the mouth pressure remain constant. This period is called the stage of "infinite possibilities," that is, the subject has no indication that the task is of limited duration, and, hence, the run might be from very short to very long. The last period, mainly the terminal four or five breaths, the stage of "exhaustion," is when the subject can no longer sustain the breathing task and

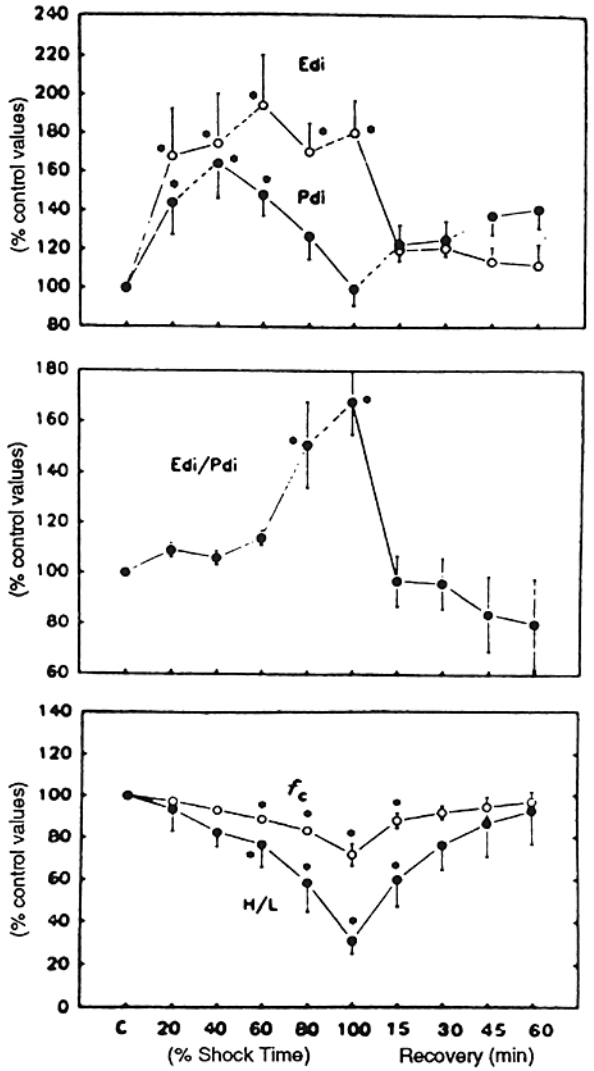


**Figure 13** Changes in the peak values of integrated spontaneous EMG activity of diaphragm (Edi) and corresponding spontaneous transdiaphragmatic pressure (Pdi; top), ratio of Edi to Pdi (Edi/Pdi; middle), and centroid frequency (fc) and ratio of high and low frequencies of diaphragmatic EMG (H/L; bottom), during shock induced by a balloon inflation in the inferior vena cava in a canine model and recovery. Means ± SE. $p < 0.05$ compared with control values. Although Edi/Pdi rose at 80 and 100% of shock time only, both fc and H/L decline immediately and progressively after decline in arterial pressure. (From Ref. 150.)

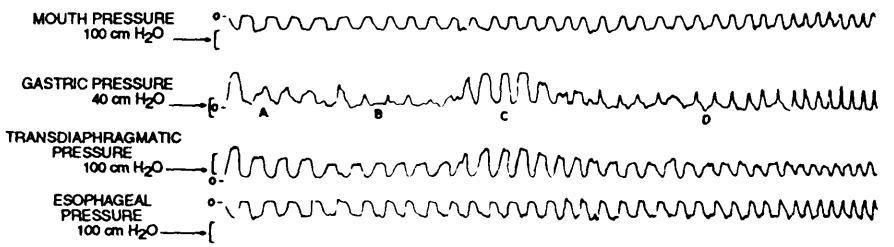


**Figure 14** Tracings of experimental run in man breathing against an inspiratory resistive load. With each breath, subject generated 75% of maximum mouth pressure. All pressures, except transdiaphragmatic pressure, were measured relative to atmospheric pressure. Only gastric and transdiaphragmatic pressure varied; mouth and esophageal pressures remained constant throughout the run. Gastric pressures increased during periods A and C and declined during periods B and D, indicating alternation of inspiratory muscle recruitment. (From Ref. 65.)

stops the effort. Between these two periods is the third period, the stage of "alternative strategies." During this period, whenever the breathing task eventually leads to exhaustion because it is above the critical level, the subject uses all possible strategies to maintain the target pressure or work to preserve ventilation. During this stage, although mouth pressure remains constant, the pleural or gastric and transdiaphragmatic pressures vary almost in an alternating fashion. These changes may be interpreted as the result of recruitment and de-recruitment between the diaphragm and intercostal/accessory muscles. This alternation has also been observed in patients breathing against a load that might lead to fatigue, as in patients who cannot be weaned from the ventilator (24). These patients also demonstrated respiratory muscle fatigue, as detected by electromyographic measurements (Fig. 15). Very early, after discontinuation of mechanical assistance, there is an increase in frequency of breathing (tachypnea), while the muscles can still generate adequate ventilation. In many of these patients, paradoxic chest wall respiration results from either inward motion of the abdominal wall (abdominal paradox) or alternating breathing (respiratory alterans) and invariably coincides with a decrease of inspiratory muscle pressure because of fatigue. Finally, if artificial ventilation is not instituted, bradypnea follows and central apnea ensues.

Tobin et al. (85), studying healthy subjects breathing against severe resistances, presented results indicating that rib cage–abdominal asynchrony and paradox are predominantly due to increases in respiratory load rather than muscle fatigue. However, even if abnormal rib cage–abdominal motion is not due to respiratory muscle fatigue per se, it may still be considered a harbinger of fatigue, since it is a direct reflection of increased respiratory load (85). The clinician then

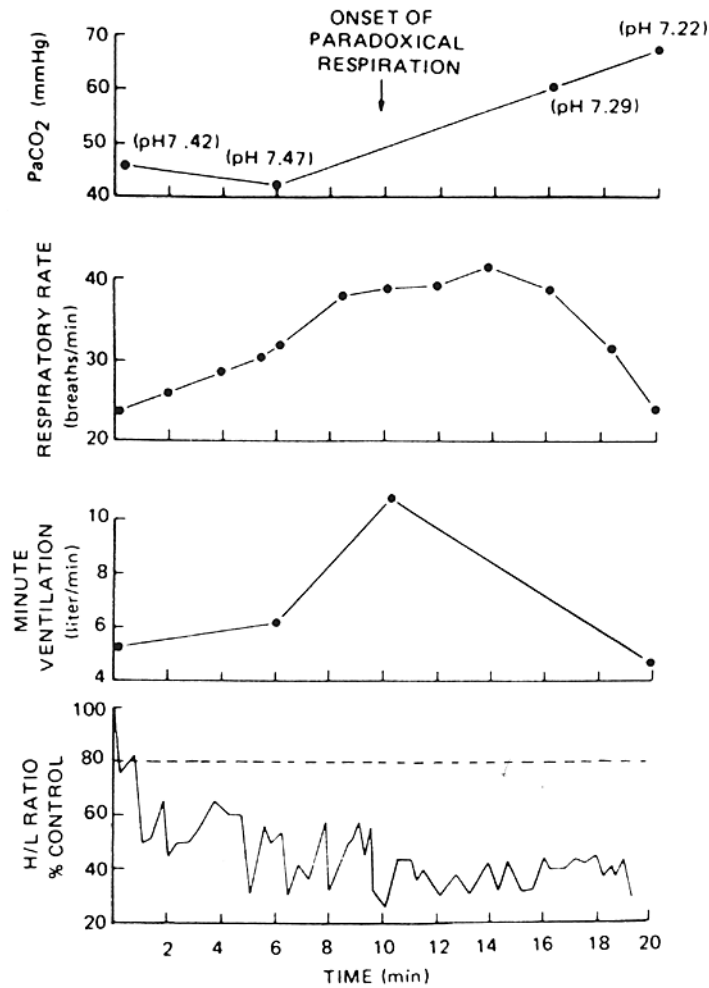


**Figure 15** Sequence of changes in $Paco_2$, respiratory rate, minute ventilation, and high/low (H/L) ratio of the diaphragm in a patient during a 20-minute attempt at discontinuation of mechanical assistance. The initial change was the fall in high/low ratio (indicating fatigue), followed by a progressive increase in respiratory rate. The $Paco_2$ fell initially, and the patient became alkalemic. Paradoxic abdominal displacements were not noted until after there had been a substantial increase in respiratory rate and minute ventilation. Hypercapnia and respiratory acidosis did not develop until after abdominal paradox and alternation between rib cage and abdominal breaths were noted. Just before the artificial ventilation was reinstituted, there was a sharp fall in respiratory frequency and minute ventilation. (From Ref. 24.)

can observe abdominal paradox and/or alternating breathing by simple inspection and/or by palpation of the chest and abdominal wall and detect excessively increased load of breathing leading to fatigue or already established respiratory muscle fatigue.

## V. Management of Respiratory Muscle Fatigue

Experimental muscle fatigue develops when the demands on the respiratory pump are excessive in relation to pump capacity. However, it is not yet clear whether in the clinical setting of ventilatory failure overt peripheral muscle fatigue develops or whether an adaptive feedback reduction of central drive avoids such fatigue, albeit at the cost of hypoventilation (1). The three components of the system (demand, capacity, and drive) are closely linked, and for the patient proceeding to ventilatory failure a small alteration in one variable may crucially determine outcome. It is rational, therefore, to direct therapeutic efforts at minimizing demand, maximizing capacity by improving contractility and endurance of the respiratory muscles, and optimizing respiratory drive.

### A. Decreasing the Demands of the Respiratory Muscles

If the work of breathing or pressure-time index increases and exceeds a critical value, the energy requirements will also increase and fatigue may develop. This may explain the inability of normal subjects to maintain high levels of ventilation for long periods (67,86,87) or to sustain normal ventilation when the work of breathing is excessive. Therefore, in patients with increased work of breathing, fatigue may be avoided by therapy if it reduces the load applied on the ventilatory pump below the fatiguing threshold. In the clinical situation, this is most often achieved by treatment directed at reducing airway resistance and increasing pulmonary compliance.

Muscle strength is an important factor of the muscle energy demands; thus pressure should be normalized by expressing it as a fraction of $P_I$max at the same fiber length. The greater the work required to sustain adequate ventilation, the greater the value of Ptidal/$P_I$max and the greater the energy demand. Thus, at constant pressure the energy demand will increase as $P_I$max decreases (71). This is of considerable physiological significance, since $P_I$max is a function of fiber length; thus, for the respiratory muscles it is determined, in part, by lung volume. Hyperinflation strongly predisposes to fatigue, not only by increasing the driving pressure, but also by decreasing $P_I$max (65,68). Furthermore, if the efficiency of the respiratory muscles decreases, which occurs with an increase in airway resistance, the $O_2$ cost of breathing and energy demands increase for the same external power (88), further predisposing to fatigue. Airway obstruction frequently leads to hyperinflation, further decreasing the efficiency of the respiratory

muscles because of the shortening of the fiber length and obliging the muscles to perform an isometric contraction in the beginning of inspiration in order to overcome internal PEEP.

### B. Improving Contractility and Endurance of the Respiratory Muscles

Rational therapy of respiratory muscle fatigue includes training, nutritional repletion, rest, and muscle pharmacotherapy. These measures prevent fatigue by improving respiratory muscle contractility and endurance and, hence, increasing their capacity. Furthermore, as the weak muscles are susceptible to fatigue, treatable or avoidable causes of weakness must not be ignored; these include hypercapnia (89,90), acidosis (91,92), hypocalcemia (93), hypokalemia, and hypophosphatemia (94), as well as thyroid, alcohol, steroid, drug-induced, and inflammatory myopathies (1).

#### *Pharmacological Agents*

Only recently has attention been focused on the effects that various pharmacological agents may have on improving the contractility and endurance of the respiratory muscles. Respiratory muscle function can be modulated pharmacologically by acting at the level of either the excitation-contraction coupling process or the energy supply to the muscles. Drugs acting at the level of excitation-contraction coupling are xanthines (69,95,96) and digitalis (97,98), while those acting by increasing the energy supply are isoproterenol (99) and dopamine (100). Studies in animals (95), isolated preparations (96,101), normal subjects (69), and patients (102,103) have shown that theophylline has a positive inotropic effect on respiratory muscles enhancing their contractility at therapeutic dose level. Hence, theophylline restored the ability of the fatigued diaphragm to generate adequate forces increasing its endurance. Its effects appear to be greater in the fatigued than in the fresh state. The mechanism of action is not yet clear, but recent studies indicate that theophylline may facilitate the influx of $Ca^{2+}$ through the slow channels and perhaps activate a $Ca^{2+}$-induced $Ca^{2+}$ release from the sarcoplasmic reticulum (104).

#### *Training*

Specific training of the respiratory muscles, like other skeletal muscles, can enhance their strength and endurance, the latter being most relevant to patients with chronic ventilatory loads or weaning difficulties. Ventilatory muscle strength has been increased by 55% in subjects performing repeated maximum static inspiratory and expiratory pressure maneuvers (87). By increasing inspiratory muscle strength, the pressure developed per breath expressed as a fraction of the maximum will diminish, thus reducing the vulnerability to fatigue.

An increase in the endurance of respiratory muscle performance has been achieved in both healthy individuals (87,105) and patients with a variety of conditions, e.g., chronic airflow limitation (106), cystic fibrosis (107), and quadriplegia (76). In quadriplegic patients (76) improvement of inspiratory muscle strength and endurance has been achieved by imposing resistive loads during inspiration for several periods each day for 6–8 weeks. Strength progressively increased over an 8-week period and endurance over a 12-week period. Leith and Bradley (87) have reported that normal subjects who spent 30–45 min/day for 5 weeks hyperventilating under normocapnic conditions were able to increase the sustainable maximum voluntary ventilation (MVV) by 14%. A 5-week period was required for MVV to return to control value after cessation of the training. However, it is well known that training produces improvements in the task being trained for, with little crossover benefit to other tasks. Further, such programs may also have substantial placebo effect (1).

The cellular adaptations that the respiratory muscles undergo during training are in all likelihood similar to those found in other skeletal muscles. Keens et al. (108) found an increase in the oxidative capacity of the diaphragm and intercostals when he chronically increased the ventilatory load in rats. Furthermore, the diaphragm responded with an increase in the proportion of muscle fibers with the myofibrillar ATPase-staining characteristics of slow-twitch fibers (108). Similarly, Farkas and Roussos (109,110) found that emphysematous hamsters increased the oxidative capacity of the inspiratory muscles while the endurance of the diaphragm increased. The diaphragm subjected to chronic hyperinflation became shorter, so its length-tension curve was shifted to the left. This adaptation was achieved by reducing the number of sarcomeres and allowing the diaphragm to operate optimally at a shorter length (109) (Fig. 16).

The literature on inspiratory muscle training leaves many clinically important questions unanswered, for example, which patients are likely to benefit from training, how much training in terms of intensity and duration produces maximal results, which training devices are most effective, and how much long-term training is required to avoid detraining. Furthermore, although training of respiratory muscles with significant reserve capacity may improve performance, training of muscles already being driven at the limit of their capacity may produce myopathic changes, well recognized in overtrained athletes, from which recovery can be prolonged (1).

### *Nutritional Repletion*

Malnutrition is a very important complicating factor in critically ill patients requiring mechanical ventilation as well as in patients with a variety of chronic lung diseases (111). It has been shown to be associated with impaired respiratory muscle structure and function in humans (112,113). Nutritional repletion can improve the strength and endurance of the ventilatory pump (1,114).

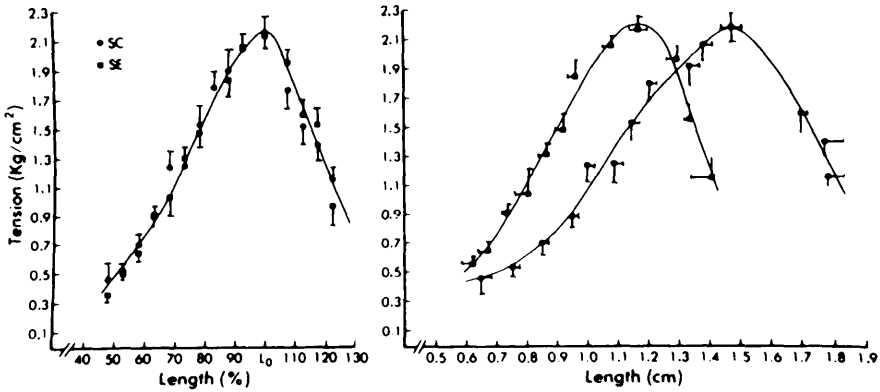


**Figure 16** Active length tension curves obtained from diaphragm strips of sedentary control (SC) and sedentary emphysematous (SE) animals. Left: tension expressed as kilograms per cross-sectional area of muscle. Both groups achieve the same $P_{max}$. Right: fiber length expressed in absolute terms. Active length tension curve of SE group is significantly shifted to the left; $P_{max}$ is generated at a shorter length in this group. (From Ref. 109.)

### *Rest*

A logical approach to restore the contractility and endurance of a muscle from fatigue would be to put the muscle at rest. Available data clearly demonstrate long-term benefit, consisting of an improvement in $Paco_2$ and maximum respiratory muscle pressures in patients with chronic neuromuscular and chest wall disorders from the noninvasive use of assisted ventilation, usually nocturnal, using both positive and negative pressure ventilators (115–121). Similarly, several studies have shown a significant improvement in patients with severe stable COPD and $CO_2$ retention, in terms of decreasing $CO_2$ and increasing the strength of the respiratory muscles, using mainly negative (122–127) pressure ventilating devices. The recent development of noninvasive positive pressure ventilation via a face or nose mask in acute exacerbations of COPD (128–130) made it possible to apply this technique to stable COPD patients (131,132). Although such mechanical ventilation rests the respiratory muscles, the mechanism whereby respiratory function, ventilatory failure, and symptoms are improved is not yet clear. The hypothesis that the improvement in these patients is a result of respiratory muscle rest reversing muscle fatigue remains speculative (1). This is because the reduction in $Paco_2$ may be due to resetting of the $CO_2$ set point resulting from the forced reduction of $Paco_2$ in the ventilation phase, and the improvement in maximum respiratory muscle pressures may be secondary to better $Paco_2$ and $Pao_2$ and to

improvement in general well-being due to better sleep and/or to resolution of cor pulmonale. In this regard, Elliott et al. (131) failed to find any relationship between the improvement in $Paco_2$ and increased inspiratory muscle strength in patients with severe stable COPD after 6 months of overnight nasal intermittent positive pressure ventilation. Since the reduction in $Paco_2$ was correlated with a decrease in gas trapping and in the residual volume, as well as with a better response to $CO_2$ rebreathing, they concluded that the improvement in blood gases was not the result of increased respiratory muscle strength consequent upon the relief of muscle fatigue, but was rather due in changes of respiratory load and central drive.

## VI. Fatigue and Respiratory Failure

### A. The Respiratory Equation

Ventilatory failure resulting in $CO_2$ retention implies alveolar hypoventilation for a given $CO_2$ production ($\dot{V}co_2$). The respiratory equation relates the arterial carbon dioxide tension ($Paco_2$) to alveolar ventilation ($\dot{V}A$):

$$Paco_2 = K\frac{\dot{V}co_2}{\dot{V}A}$$

where K denotes the constant of proportionality. Since $\dot{V}A = \dot{V}E - \dot{V}D$, where $\dot{V}E$ denotes minute ventilation and $\dot{V}D$ dead space ventilation, the respiratory equation may be expressed as follows:

$$Paco_2 = K\frac{\dot{V}co_2}{\dot{V}E - \dot{V}D} = K\frac{\dot{V}co_2}{\dot{V}E(1 - \dot{V}D/\dot{V}E)}$$

$$= K\frac{\dot{V}co_2}{\dot{V}E(1 - fVD/fVT)} = K\frac{\dot{V}co_2}{\dot{V}E(1 - VD/VT)}$$

$$= K\frac{\dot{V}co_2}{VT \cdot f(1 - VD/VT)}$$

This equation states that $Paco_2$ will rise if carbon dioxide production increases without increasing alveolar ventilation or when for a given carbon dioxide production ($\dot{V}co_2$) alveolar ventilation decreases by virtue of a rise in the ratio of VD/VT (either by increasing VD or decreasing VT)at a constant total ventilation ($\dot{V}E$ or VT·f), when minute ventilation decreases at constant VD/VT, or both. An important point that may be deduced from this equation is that at constant $\dot{V}E$, $CO_2$ may rise by increasing the frequency, with a concurrent fall in tidal volume and hence increase in VD/VT. The $\dot{V}E$ in the above equation may further be separated to its two components, namely, inspiratory flow and duty cycle:

$$\dot{V}_E = V_T \cdot f = V_T \frac{1}{T_T} = \frac{V_T}{T_I} \frac{T_I}{T_T}$$

where $T_I$ is inspiratory time.

Thus, a reduction in mean inspiratory flow ($V_T/T_I$), duty cycle ($T_I/T_T$), or both will cause retention of carbon dioxide. In these equations it becomes apparent that $Paco_2$ may rise due either to inability of the muscles to generate pressure and, in turn, inspiratory flow ($V_T/T_I$), or to alterations in the pattern of breathing ($f,T_I/T_T$), or even to reduced neural output. As fatigue ensues, the last two mechanisms of $CO_2$ retention might be implicated either as an adaptation to the altered characteristics of the respiratory muscles via a feedback loop or as central fatigue.

### B. Fatigue as Cause of Respiratory Failure

In a number of conditions, as in cardiogenic (Fig. 3) and septic shock (Fig. 4) in dogs or in patients during the weaning period from ventilators (Fig. 15), respiratory muscle fatigue is recognized as a cause of respiratory failure, whereas in other conditions it is very likely that patients hypoventilate due to fatigue. Because hypercapnia occurs either acutely, as in cardiogenic shock with pulmonary edema, or chronically, as in chronic obstructive pulmonary disease, it follows that if fatigue plays a role in the $CO_2$ retention, it may occur either acutely or chronically.

#### *Acute Hypercapnia*

Fatigue and, in turn, hypercapnia of acute onset are usually due to a combination of increased mechanical load of the lung, reduced muscle strength, decreased efficiency, and reduced energy supplies to the inspiratory muscles. The mechanisms responsible for $CO_2$ retention are both decreasing $\dot{V}_E$ and increasing $V_D/V_T$. The sequence of events and their potential explanation is as follows: The patients with weak and/or loaded respiratory muscles by decreasing inspiratory time reduce tidal volume in order to diminish Ptidal and the energy demand per breath (expressed by the pressure-time index, PTI). In addition, with this strategy the respiratory muscles operate at an optimal length and will not substantially affect its geometry, since large tidal breaths force the muscles to shorten more than the small tidal breaths. This reduction in $V_T$ is compensated at least at the beginning by increasing breathing frequency so that minute ventilation is maintained or increased. In consequence, since such a pattern of breathing increases $V_D/V_T$, $Paco_2$ will increase if $\dot{V}_E$ is preserved or may remain stable if $\dot{V}_E$ is increased proportionately. Such a frequency of breathing, however, is no longer optimal and for the same alveolar ventilation the energy demand will increase. Thus, although the nonoptimal frequency seems to be a better option than the long

$T_I$, coupled with the inadequate energy supply it will finally lead to muscle fatigue. Pressure will then decrease, and as a result $V_T$ and $\dot{V}_E$ will decrease while $V_D/V_T$ further increases. The reduction in pressure will obviously decrease the PTI and energy demands per breath, but alveolar ventilation ($\dot{V}_A$) will be further reduced and $Paco_2$ will rise. At a later stage (for example, in patients during weaning failure or in animal models with shock) via central mechanisms, $T_I$ increases again and respiratory frequency gradually decreases, resulting in drop of $\dot{V}_E$ (23,24). Finally, at extreme fatigue, the CNS reduces the output signals per breath, further reducing tidal pressure and $V_T$, eventually leading to respiratory arrest.

In asthma and exacerbations of COPD, which are common causes of acute hypercapnic respiratory failure, severe airway obstruction results in reduction of dynamic compliance and in rapid, shallow breathing. These factors increase the work of breathing and the energy demand, leading to breathlessness and potentially to fatigue. The latter is a very probable hazard, as hyperinflation to achieve adequate gas exchange can be severe; the strength and efficiency of muscles under these conditions are reduced. At the same time the required pressure per breath (Ptidal) is increased excessively due to auto-PEEP, high elastic and resistive inspiratory load. Hyperinflation predisposes maximum inspiratory pressure ($P_I$max) to decrease and, hence, Ptidal/$P_I$max to increase, leading potentially to fatigue (Fig. 17). The blood supply eventually may be impaired as muscular contractions become very strong in order to maintain higher end-expiratory lung volumes (134). Finally, severe lung disease may lead to hypoxemia and may reduce the amount of energy available, resulting in lactic acid production (135). A constellation of factors predisposes maximum inspiratory pressures to decrease and, hence, Ptidal/$P_I$max to increase, leading to dyspnea, fatigue, or both. Such a situation causes alveolar hypoventilation by reducing tidal volume, either as a protective mechanism for the muscles or as a consequence of failure (fatigue) of the muscles. It must be noted that, because of hyperinflation, values of Ptidal/$P_I$max lower than that needed in FRC, i.e., about 0.50 (65), are adequate to lead the inspiratory muscles to fatigue.

Muscles that are used most often, such as the inspiratory muscles (particularly the diaphragm), atrophy the fastest. Artificial ventilation may be followed by weakness of the inspiratory muscles due to atrophy (secondary to disuse). Thus, it is probable that patients who failed to wean suffer from disease atrophy, which leads to shortness of breath and fatigue (24). In addition, after prolonged stays in the intensive care unit, patients often suffer from malnutrition, which clearly affects both muscle strength and ventilatory drive (93,113,114,136–138).

In most neuromuscular diseases with acute onset (e.g., diaphragmatic paralysis, poisons such as organophosphates), weakness of the respiratory muscles is a very common feature leading to ventilatory failure. In such conditions, the remaining normal muscle cells cannot develop sufficient force to maintain adequate

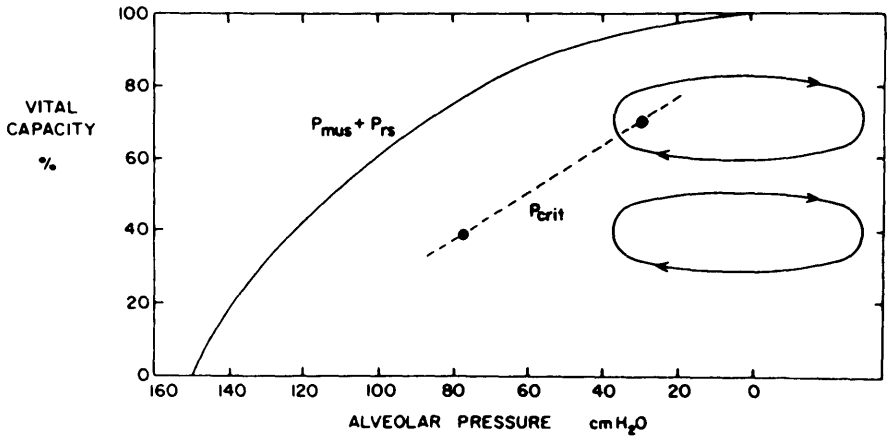


**Figure 17** Maximum inspiratory pressure–volume diagram. Maximum inspiratory pressure of respiratory system at different lung volumes is given by solid curve (Pmus + Prs). Dashed line joins two critical values (Pcrit) measured at FRC and FRC + one-half IC. At these two lung volumes, two hypothetical alveolar pressures do not attain Pcrit; at FRC + one-half IC, Pcrit is exceeded. (From Ref. 65.)

alveolar ventilation and hypercapnia ensues. This may be the result of CNS adaptation, muscle fatigue, or both. It is apparent that the clinical expression of failure (acute vs. chronic) depends on the nature of the underlying disease. It may vary from rapid onset, as in Guillain-Barré syndrome, to stable chronic failure, as in longstanding poliomyelitis. The latter group is extremely vulnerable to acute failure, compounding their chronic failure under a variety of conditions (e.g., infection, $CO_2$ production, sedation, anesthesia, surgery).

In cardiogenic shock there is an increase in energy demand (stiff lungs, hyperventilation) and a decrease in the supply of blood to respiratory muscles. In such a disease state, the respiratory muscles may fail. The condition is well described in animal models; respiratory muscle fatigue leads to severe alveolar hypoventilation and is followed by bradypnea and respiratory arrest (23). Early mechanical ventilation prevents this from occurring; blood flow is redirected from respiratory muscles and diverted to vital organs, while lactate production is minimized (139). In noncardiogenic pulmonary edema, patients need increased pressure and energy to ventilate the lungs. Coexisting severe hypoxemia due to lung damage may diminish the energy supply to the muscles; furthermore, weakness of the respiratory muscles may be present as a result of malnutrition or sepsis. This imbalance between capacity of the ventilatory pump and demands made upon it lead again to alveolar hypoventilation.

### *Insidious Onset of Hypercapnia*

Patients who retain $CO_2$ insidiously invariably need to generate high pressure per breath that is a large fraction of their maximum inspiratory pressure. The pressure is generated to overcome forces imposed by the chest wall (kyphoscoliosis, thoracoplasty, pleural thickening, severe obesity), by the lung (bronchitis, emphysema, bronchiectasis), or by both (scleroderma, polymyositis). In a category of patients, although Ptidal is normal, it may be a large fraction of $P_I$max, since the latter is reduced (neuromuscular disorders). It is difficult to ascertain the mechanism of $CO_2$ retention in such patients. However, reduction of VT is a frequent feature and, therefore, may be the common pathway to $CO_2$ retention by increasing in VD/VT. Two alternative pathways are proposed, which are not mutually exclusive. As disease progresses, the pressure, PTI, or power required to maintain adequate ventilation is increased and the muscles become more vulnerable to dyspnea and fatigue. In this process, the CNS may set a lower level of ventilation or may alter the pattern of breathing in order to avoid dyspnea or exhaustion. Alternatively, it is possible that the ventilatory pump becomes chronically fatigued (centrally or peripherally), so decrease in alveolar ventilation is the result of pump failure. Both mechanisms may be operative.

When COPD patients who retain $CO_2$ were compared to those who did not retain $CO_2$, it was found that VT and TI were reduced in the $CO_2$ retainers, while frequency was increased (140). At equal minute ventilation, VD/VT was higher in the $CO_2$ retainers and, hence, $CO_2$ increased. The increased VD/VT may be explained as follows: Patients who retain $CO_2$ have lower $FEV_1$ and $P_I$max values, higher effective impedances and higher weights, functional residual capacities (FRCs) and FRC:total lung capacity (TLC) ratios than do nonretainers of $CO_2$ (140,141) (Fig. 18). At equal driving force (PO.1) such a patient is better off terminating TI early, thus avoiding substantial deviation from optimal length and perhaps avoiding substantial geometric alterations of the diaphragm and intercostal muscles, than taking a large VT (long TI). In the latter case, at the end of inspiration, this type of patient may have to develop pressure that approaches or exceeds the "critical" inspiratory pressure, leading to severe dyspnea or fatigue. In fact, although hypercapnia can be reduced in COPD patients by voluntary changing the breathing pattern (i.e., increasing VT and decreasing frequency), it has been shown that this type of breathing brings about fatigue of the inspiratory muscles and that the imposed pattern cannot be tolerated more than a few minutes (142). In this regard, patients with COPD and severe hypercapnia developed a mean Ptidal that was 27% of $P_I$max, whereas the Ptidal in patients with no $CO_2$ retention was only 10% of $P_I$max (141). Using the results from normal subjects in which the critical pleural pressure for developing fatigue at FRC plus one-half inspiratory capacity is 25–30% of the maximum (65), we may place $CO_2$ retainers above or in the critical zone of fatigue, whereas nonretainers remain in the

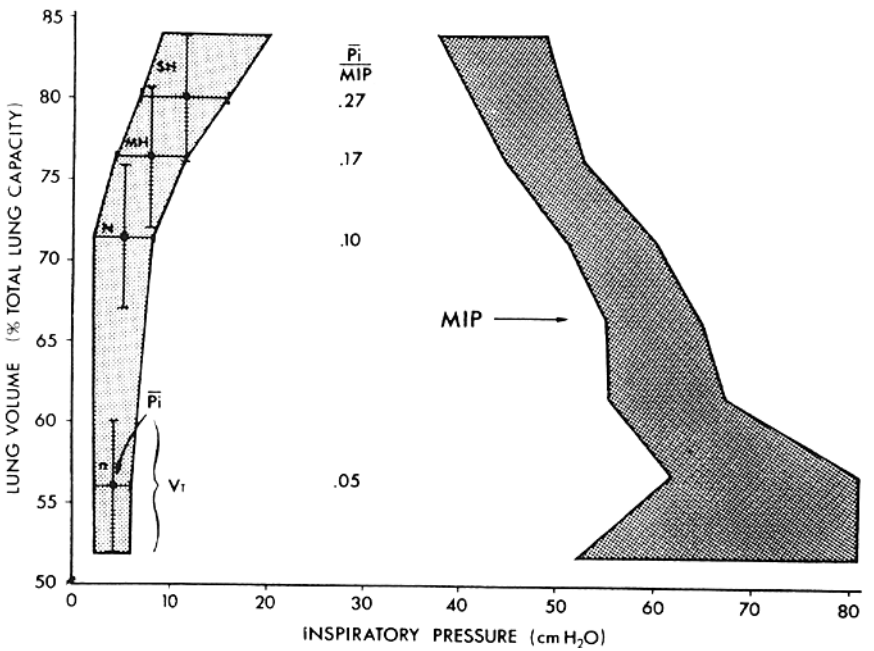


**Figure 18** Relationship among lung volume, tidal pressures, and maximal inspiratory pressures (MIP) in the normocapnic and hypercapnic groups of patients with COPD. The right band is drawn from MIP values plus 95% confidence intervals obtained at FRC in all patients and plotted against their FRC/TLC values ($r = 0.32, p < 0.001$). On the left, vertical bars represent the tidal volume ($V_T$) excursions and horizontal bars represent the mean (± SD) inspiratory transpulmonary pressure swing (Pi) for the normocapnic, moderately hypercapnic and severely hypercapnic groups. A subgroup of 15 patients from the normocapnic group who have the smallest FRC/TLC, with values near normal, is shown in the left lower corner. The left band connects the SD values for each group. The inspiratory muscle load (Pi/MIP) for each group is given at the level of their midinspiratory volume. (From Ref. 141.)

nonfatiguing zone (Fig. 19). In patients with COPD and $Paco_2$ less than 45 mmHg, this was especially evident. The Ptidal/$P_I$max was 10%, and the residual volume (RV)/TLC ratio 50% (141); that is, the tidal inspiratory pressure was certainly below the critical zone for developing fatigue. In contrast, in patients whose RV/TLC was 67% and who retained $CO_2$, Ptidal/$P_I$max was 27% (141)—a value highly probable to predispose the muscles to fatigue. Thus, in some patients the combination of increased work of breathing due to lung disease and/or obesity, decreased mechanical efficiency due to hyperinflation and/or airway resistance, and muscle weakness due to hyperinflation and/or atrophy and undernutrition

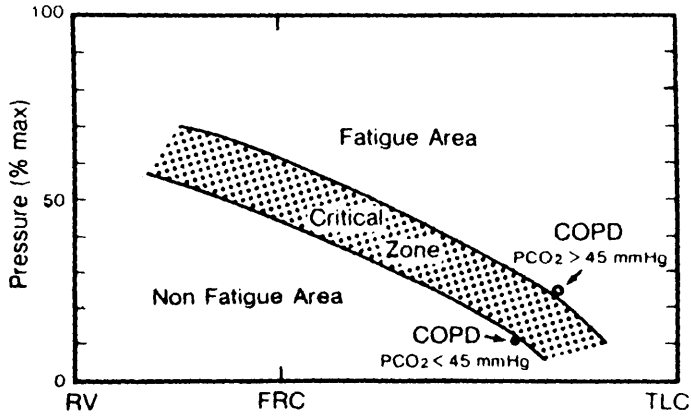


**Figure 19** Effect of lung volume on critical pressure of the respiratory muscle. Diagram is constructed from findings in normal subjects breathing against high inspiratory resistance. Subjects who, at functional residual capacity (FRC) or higher (lung volume), generate per-breath pressure (mouth and/or transdiaphragmatic) above the critical zone become fatigued; in contrast, in subjects whose pressure is below the critical zone, fatigue does not occur. Note that patients with chronic obstructive pulmonary disease (COPD) and $CO_2$ retention ($P_{CO_2} > 45$ mmHg) are above or barely in the upper limit of the critical zone, whereas patients with no $CO_2$ retention ($P_{CO_2} < 45$ mmHg) are below or barely in the lower limit of the critical zone. RV = residual volume; TLC = total lung capacity. (From Ref. 151.)

pushes the respiratory muscle to the limits. In such a predicament, there are two alternative pathways. First, the central controllers (via a feedback mechanism) reduce the $T_I$ and $V_T$ and, hence, the Ptidal. Thus fatigue is avoided. If it is so, hypercapnic subjects weigh their options and choose hypoventilation rather than respiratory muscle fatigue (141). Second, the muscles pass into a stage of chronic failure (fatigue), leading to reduction in the driving pressure and $V_T$. As previously discussed, the hypothesis that the improvement in daytime hypercapnia and maximum respiratory muscle pressures observed in patients with severe stable COPD using various nocturnal ventilating devices is a result of respiratory muscle rest reversing muscle fatigue remains as yet speculative. These authors favor the first strategy, and we speculate that afferents from the small fibers (types III and IV) stimulated by the heavy work (ergoreceptors, type III) or by noxious substances like lactic acid (nociceptors, type IV) modify the CNS output. The mechanism is not known, but the production of endogenous opioids may play an important role.

In many other diseases characterized by the presence of chronic hypercapnia (e.g., severe obesity and kyphoscoliosis), the mechanism leading to $CO_2$ retention is the same or similar with that in COPD patients. In fact, patients with

severe obesity sometimes experience hypoventilation; the syndrome is called obesity hypoventilation syndrome. The pathophysiological mechanisms of this syndrome are multiple. Obesity sufficient to increase body weight by 50% or more increases the work of breathing, in part through mass loading of the chest wall and in part through secondary effects that reduce lung compliance (143). In addition, these patients appear to have somewhat weaker than normal (by about 30%) respiratory muscles (144). It is intuitively logical that the combination of decreased respiratory system compliance plus respiratory muscle weakness and hypoxemia may lead to an increase in Ptidal/$P_I$max and, therefore, through the same mechanism as in COPD patients, to a decrease in VT and alveolar ventilation.

Patients with kyphoscoliosis may progress to hypercapnic (and hypoxemic) respiratory failure with cor pulmonale. There is no clear consensus as to which specific characteristics reliably predict such a progression, although the degree of spinal distortion plays a significant role. Kyphoscoliosis distorts the spine and rib cage, thus changing the position and length of the diaphragm and intercostal muscles. The work of breathing and oxygen cost of breathing are increased markedly (145), $P_I$max is reduced (148), respiratory compliance may be reduced severely, and atelectasis may be prominent. Recent studies have shown that sleep-related abnormalities may influence significantly the clinical course of patients with kyphoscoliosis (147,148). Nocturnal hypoventilation and decreased arterial oxygen saturation may be due to reduced chest wall movement or obstructive apneas (147,148). Hence, recurrent hypercarbia and hypoxemia during sleep may set in motion or potentiate the development of hypercarbia, cor pulmonale, and respiratory muscle dysfunction (148).

### *Conclusions*

Inability of the respiratory muscle to generate pressure because of fatigue, leading to ventilatory failure, is well documented only in shock. For the remaining patients with hypercapnia, acute or chronic, the evidence is not as clear. The favored hypothesis is that, as Ptidal becomes a large fraction of $P_I$max, the breathing work load increases (e.g., decreased lung and/or chest wall compliance), $P_I$max is reduced (e.g., neuromuscular disease, hyperinflation), or both occur (e.g., acute asthma attack). Inspiratory time is reduced thereby, and a decrease in VT follows. This strategy possibly involves the small afferents (III and IV) from the muscles and the endogenous opioids, avoids high values of Ptidal, and therefore minimizes dyspnea and eventually fatigue. Fatigue may occur if this strategy fails.

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# 7

# Control of Respiration in Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

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Un homme qui se noie se raccroche à tout, même à un serpent.

## I. General Considerations

We will define the respiratory control system as the assembly of all mechanisms capable of causing active adjustments in quantity or style of ventilation or gas transport. These mechanisms include specific reflexes from identified receptors, more complex stereotyped autonomic and somatic motor responses to certain stimuli, and alterations in respiration arising from emotions or conscious effort. The recognized functional components of the control system are detailed in Sections IV–VIII.

In acute respiratory failure (ARF), the respiratory system is deranged in a wide variety of different ways. Blood gases are abnormal. Gas exchange, pulmonary circulation, chemical feedback systems, muscle fiber environments, mechanical load on the muscles, sensory feedback from the lungs, left ventricular function, central nervous system function, electrolytes, and nutrition are usually abnormal. The system is unstable in a variety of ways. Muscles may be fatigued, leading to a downward spiral of decreasing ventilation. Hypoxia and acidosis increase the

probability of a fatal cardiac arrythmia. Impaired cerebral function reduces the patient's ability to make logical life-preserving decisions. Small variations in quantities whose values can normally range rather widely and be tolerated may now set off chains of interacting processes that can lead to worsening of the condition or death. The problem of an ideal control system in these extreme conditions should be to make all adjustments within its means to arrive at the combination of variables that fits with the most stable state possible in the circumstances.

The following are some of the questions that physiologists have tried to answer with respect to acute respiratory failure:

What are the important control mechanisms, and how do they work normally?

Do these mechanisms continue to work "normally" in this extreme condition?

Is the behavior of the control mechanisms, individually or collectively, optimal?

Would the patients be better off if they adopted a combination of respiratory variables different from the one they are driven to adopt by their own control system?

Most of these questions are only partly answered and much remains to be learned. In particular, the ability to understand complex interactions between components of a multicomponent control system is very limited. The best attempts to understand the control system have focused on a particular variable and considered how the system controls that variable. To a limited extent, the influence of a second or third variable can then be considered by looking at how it affects control of the first variable.

In analyzing the behavior of the respiratory control system, physiologists usually make a tacit assumption that the system has been endowed with a sense of purpose, usually, in a general way, to maintain homeostasis. The questions listed above about the control system assume the purpose of the respiratory control system in acute respiratory failure is to maximize the chance for the patient to survive the acute episode of deteriorating respiratory function. Many discussions of respiratory control use language that implies the belief that the control system has an intelligence of its own. We talk of a system that responds to imposed problems, that adopts a strategy, that behaves well or poorly, that has wisdom or is stupid, that "can't" or "won't" breathe, or that has certain aims or objectives. While these words are sometimes useful for focusing ideas, and some of them appear in this chapter, we consider the respiratory control system to be no more than an assembly of neutral circuits, receptors, and effectors that happen to have an influence on respiration. Its components and their behavior have no doubt evolved under the pressures that drive species toward forms that increase the

likelihood of survival. It does not seem probable however, that evolutionary pressure would yield an integrated mechanism that was particularly adapted to save humans from the damage caused by cigarette smoking and behaved as if it was intelligently trying to do so. Instead it makes sense to look at the control system as if it were simply a set of interacting control systems, each with a different "purpose," by which we mean that each behaves in such a way that it tends to stabilize some important physiological variable that we can define.

In this chapter, we will first outline the problem faced by the control system. Then we will outline the general framework linking the main respiratory variables, as a basis for thinking about the control system. Third, we will examine control as viewed from several quite different points of view, each focusing on stabilization of a particular aspect of the system, namely blood gases, respiratory muscles, the lungs themselves, oxygen delivery, and the comfort of the nervous system. Finally, we will discuss interactions between these points of view and review the data about how the system actually behaves in chronic obstructive pulmonary disease (COPD) in acute respiratory failure (ARF).

## II. The Problem Imposed on the Control System

Derangements of the ventilatory and circulatory system in COPD in the chronic and acute states are described in detail in the chapters on gas exchange, lung mechanics, respiratory muscles—action and mechanics, fatigue and limits, left ventricular function, nutritional evaluation, and cardiopulmonary interaction in this book. A simple list of the abnormalities (Table 1) emphasizes the extent and complexity of the derangement in function. Separate control systems have been described for many of the variables mentioned in the table. Many of these control systems also have an influence on other variables and other control systems.

## III. Theoretical Framework

### A. Normal Ventilatory Control

The cells and organs of mammals function best when the fluid milieu in which they are immersed has a pH of 7.4, a $P_{CO_2}$ of 40 mmHg, and a sufficient partial pressure of oxygen to support aerobic metabolism. Cellular metabolism consumes oxygen and produces $CO_2$, whose concentration tends to increase both inside and outside the cells together with $[H^+]$. In order to keep $P_{CO_2}$ and $[H^+]$ constant, the gas transport system of the body must remove $CO_2$ from cells at the same rate the gas is produced. When there is a change in rate of $CO_2$ production ($\dot{V}_{CO_2}$), the gas transport system must be controlled so that the rate of $CO_2$ gas transport always perfectly matches the rate of $CO_2$ production. An ideal control system for ventilation, therefore, would adjust $\dot{V}_A$ (alveolar ventilation) continuously so that the

**Table 1** Physiological Variables that May Be Deranged in COPD in ARF

- Gas exchange
  - High $V_D$ and $V_D/V_T$ ratio
  - Increased proportion of low $\dot{V}/Q$ regions, increased $Q_S/Q_t$
- Lung mechanics
  - High airways resistance
  - Expiratory flow rates severely limited
  - High FRC
  - High dynamic elastance
  - Intrinsic PEEP
- Respiratory muscle mechanics
  - Reduced operating length of inspiratory muscles
  - Reduced mechanical advantage of inspiratory muscles
  - Altered synergism of respiratory muscles
  - Hypertrophy or atrophy of respiratory muscles
- Respiratory muscle fatigue
  - Muscles operating close to fatigue threshold
    - Higher inspiratory pressures $PEEP_i$, $R_{aw}$
    - Lower maximum pressures
    - Length and mechanical advantage problems, weakness, atrophy from nutritional deficit, metabolic disorders
  - Low $O_2$, high $CO_2$, high $H^+$
  - Inadequate blood supply
- Cardiac output
  - Coincident coronary artery disease
  - Afterload to RV, LV
  - Preload to RV, LV
  - Oxygenation, $H^+$, metabolic derangements
- Sensations
  - Sensory input from muscles, lungs, joints, and upper airways, appreciated as dyspnea, pain, or other discomfort
- Blood gases
  - Hypoxemia
  - Acidosis
  - Hypercapnia
- Controller
  - Brainstem/chemoreceptors
    - Primary CNS disease
    - Altered function secondary to prolonged hypoxemia, hypercapnia
    - Altered cerebral blood flow
    - Altered neural function due to acute hypoxia, acidosis, alkalosis, drugs, sleep deprivation
  - Intellect
    - Somnolence
    - Disorientation
    - Impaired judgment

**Table 1** (Continued)

| |
|---|
| Controller (continued) |
| Emotions |
| Fear |
| Anxiety |
| Depression |
| Metabolic rate |
| Nutrition |
| Work of breathing |
| Fever |
| Oxygen delivery, limited oxygen consumption |
| Blood chemistry |
| Hypomagnesemia |
| Hypokalemia |
| Hypophosphatemia |
| Drug effects |

ratio ($\dot{V}CO_2/\dot{V}_A$) was kept constant, $CO_2$ was cleared just as quickly as it was produced, and $PCO_2$ was kept perfectly constant.

In fact, humans and other mammals are provided with a nearly ideal ventilatory control mechanism. $\dot{V}CO_2/\dot{V}_A = PCO_2$ is held almost perfectly constant in the face of the huge variations in $\dot{V}CO_2$ that occur in exercise, or major changes in mechanical load on the respiratory pump, or major weakness of respiratory muscles. In spite of extensive investigation, we remain uncertain about the mechanism by which this is achieved. Many mechanisms with some potential to control ventilation have been identified and can be tested, and they will be discussed in the following sections. Most of them depend on the concept of negative feedback, which implies that there are sensors that detect a discrepancy between ideal and actual ventilation and convey this error signal to the controller, where it instigates a corrective action. In most cases we are unable to measure the error signal or, as in the case of blood gases in exercise, can measure it but find it is zero or negative, the controller having made its adjustment without benefit of this information. Until this basic process is understood, no discussion about control of respiration in disease can hope to arrive at a real understanding. In this chapter we try only to provide a framework for thinking about control of breathing in COPD.

### B. Components of the Respiratory Controller

Figure 1 is a conceptual working diagram of the respiratory controller. Although some components of the diagram correspond more or less to anatomical entities, they are defined in practice by stimulus-response experiments designed to study

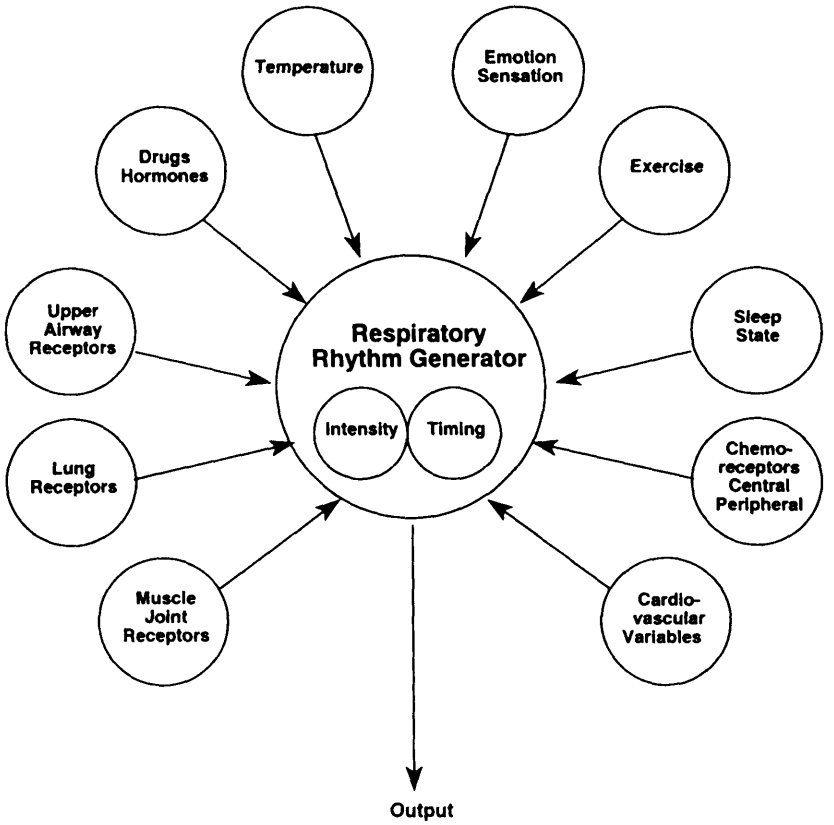



**Figure 1** Conceptual scheme of components of the respiratory controller.

their behavior. Summaries of evidence for the existence of the various components can be found in standard references (1–3).

### C. Negative Feedback Control Theory

The most commonly used basic conceptual model for homeostatic mechanisms is simple negative feedback. Such a model has the components shown in Figure 2 (4).

In a typical example, a house with a furnace and a thermostat, the controlled system is the internal environment of the house and the controlled variable is the temperature. A thermometer measures the temperature and feeds back a corresponding signal to a device that compares that signal with a desired value corresponding to ideal temperature. Any difference between the two results in an error

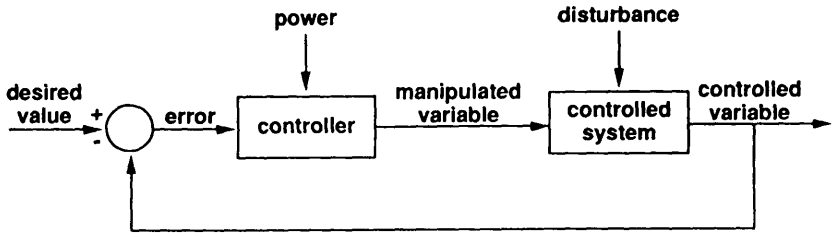



**Figure 2** Block diagram of a feedback control system. (For explanation see text.)

signal that activates the controller, in this case the throttle of the furnace, which changes the manipulated variable, which is the heat production by the furnace. In this way, heat production by the furnace is made to match heat loss from the house when a disturbance such as a change in external air temperature or wind velocity tends to change that temperature.

In the respiratory system, negative feedback modeling has been extensively applied to chemical control of ventilation. Here the controlled system is the lung gas exchange organ and the controlled variable is usually taken as $P_{a}CO_2$. The feedback is through arterial and brainstem chemoreceptors. The reference standard $P_{a}CO_2$, or set point, is somehow maintained in the brainstem. The controller is the whole system of respiratory centers, spinal cord, peripheral nerves, and muscles that produce alveolar ventilation, which is what determines the rate at which $CO_2$ is exhaled from the lungs. The system is designed to stabilize $P_{a}CO_2$ in the face of fluctuations in $CO_2$ production.

The concept of negative feedback control is very powerful and provides the basis for our understanding of homeostasis, but its application in quantifiable detail is often problematic. The respiratory system is obviously more complex than a simple linear feedback system. (There are multiple respiratory chemoreceptors, for example, with different response characteristics, sensitive to either arterial or brain interstitial values of blood gases, each with different, alinear response characteristics, and each capable of influencing ventilation.) Respiratory variables may be controlled more exactly than predicted by simple negative feedback theory using proportional control in which the greater the value of disturbances, the greater the steady-state error. In that case more elaborate theories may be proposed, involving 'integral control' in which controller output continues to change in response to a disturbance until the controlled variable is exactly the same as the set point, or "rate control," in which the controller output varies according to the rate of change of the controlled variable (4). "Feed forward" control, in which the disturbance (e.g., $\dot{V}CO_2$) is measured and the controller adjusts its output directly to match the disturbance, has also been invoked to explain stability of blood gases. For respiration, the chemical control system and vagal volume receptor feedback

are the only ones that have been studied extensively enough to justify analysis of the detailed operation of the controller characteristics. For the vagal system most of the data comes from other mammals and may not be applicable in detail to humans. For the most part, nonquantitative ideas of simple negative feedback underlie thinking about control systems for respiration from conscious sensations, cardiovascular receptors, lung receptors, and muscle receptors.

### D. Defining and Measuring the Output of the Controller

The simple controller diagram for respiration, analogous to Figure 2 (see Figure 6) includes an element that receives a signal indicating how far the chemoreceptor measurement is from its reference value and has ventilation as its output. The physiological reality is much more complicated (Fig. 3). In fact, afferent information from chemoreceptors is fed into a complex and poorly defined neural network that generates the respiratory rhythm and sends its output to motoneurons in the spinal cord. There the signal is modified by spinal reflexes and other inputs to the motoneurons and emerges as a set of signals in the multiple motor nerves that supply diaphragm, intercostal, neck accessory, abdominal, upper airway, and other, synergistic muscles. These muscles are activated at various phases of the respiratory cycle and create tension that depends on the size, length, and velocity of shortening of each muscle. The tension in each muscle contributes to muscle pressure (Pmus) to a degree that depends on the mechanical advantage of the muscle at the time. The pressure overcomes the resistance and elastance of the respiratory system to produce ventilation ($\dot{V}_E$). Deadspace and tidal volume/frequency relations govern the relation between $\dot{V}_E$ and alveolar ventilation. When output of the controller is assessed by measuring $\dot{V}_E$, it must be recognized that an increase in output does not simply indicate the effectiveness of stimulation (for example chemoreceptor sensitivity), but depends as well on the effectiveness of all the steps required to transform the stimulation into ventilation. In COPD, there may be pathological alterations in all of the steps between stimulation and $\dot{V}_A$. Attempts to assess the output have therefore tried to bypass some of the steps by intercepting the signal higher up in the chain than at ventilation or have tried to correct for the decreased effectiveness by some normalization procedure.

#### *Pressure Measurements*

To eliminate the step of conversion of pressure to ventilation, pressure itself can be measured or calculated. It does not suffice to simply measure intrathoracic pressure through the respiratory cycle because the same muscles activated in the same way can make quite different intrathoracic pressures, depending on the load (resistance and elastance) that they face. Instead, it is necessary to consider the pressure they would generate under a standard loading condition, ideally an isovolume, isoconfiguration, isometric contraction.

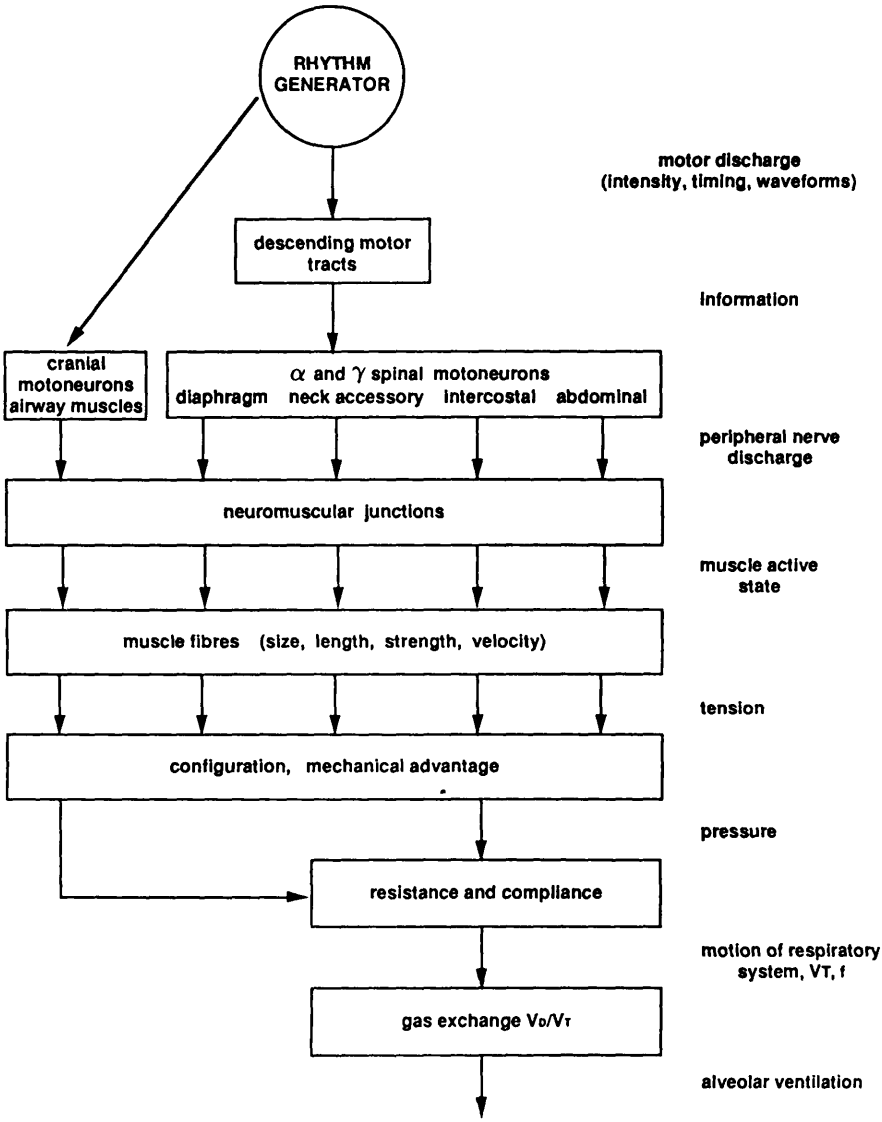



**Figure 3** Diagram of the chain of transformations through which the information contained in discharges of the central respiratory rhythm generator is changed into alveolar ventilation. The rectangular blocks indicate anatomical components or physiological constants that govern the transformation of information from one form to the next. On the right side are listed the forms the information takes at various stages where it might be monitored and evaluated.

One approach is to occlude the airway just before the beginning of inspiration and measure the pressure generated in the airway or in the pleural space with inspiration (5). This "occlusion pressure" technique has been used by many authors to assess controller output in COPD. There are both practical and theoretical difficulties with the method, discussed in detail in a recent review (6). Important practical problems are the scatter in repeated measurements when only the first 100 msec of inspiratory pressure is used ($P_{0.1}$) and damping of the pressure signal during transmission to the upper airways when mouth pressure is used (7,8). Theoretical problems are: motion of the chest wall during occluded inspiration, which renders the contraction nonisometric, phase lags between intrathoracic pressure and airflow (especially in COPD), altered phase relations between the intrathoracic pressure and the activity of inspiratory muscles, and possible changes in the shape of the wave of intrathoracic pressure, and therefore in the relation between $P_{0.1}$ and the magnitude of the pressure wave at other times in the breath. Nevertheless, occlusion pressure can give reasonably accurate measurements of the rate of rise of pressure at the beginning of inspiration in COPD, as shown by Murciano et al. (8). Pressure measured through an endotracheal tube is a more reliable indicator of intrathoracic pressure than mouth pressure, which is damped by filtering in the upper airway. From tracheal occlusion pressures we believe it is plausible to infer either estimates of overall pressure output or changes in shape of the output wave.

A second approach is to calculate the time course of respiratory output through the breath as a standardized isometric muscle pressure (Pmus). This is done from measurements of flow, volume, resistance, and compliance and from assumptions, based on measurements in normal humans, about pressure losses due to force length and force velocity (9–11). This approach has not yet been applied to the analysis of control in COPD patients.

It is important to point out that both these pressure measurements give estimates of the output of the actual muscles of the patient. At their theoretical best in COPD patients, they give pressures that are lower than they should be for any degree of motoneuron output, because the muscles of the overinflated chest have a reduced mechanical advantage, may be at less than their optimal length, and may be impaired by poor nutrition, hypoxemia, hypercapnia, acidosis, metabolic derangements, insufficient blood supply, or fatigue (see Chapters 5 and 6) although compensation by hypertrophy or reduction in number of sarcomeres per fiber can compensate for some of these disadvantages (12). In COPD it can be assumed that any pressure measurement, however valid, gives an underestimate of respiratory lower motoneuron output.

### *Direct Assessment of Motoneuron Output*

Quantitative electromyograms (EMG) measure intensity of electrical activity of the muscles, which corresponds to intensity of electrical activity of motoneurons.

In normal subjects, in isometric contractions, EMG quantified in the standard way is proportional to tension generated by a muscle. The difficulty of applying this technique to assessment of respiratory motor output is partly practical and partly theoretical.

The practical problem is one of standardization. The amplitude of any EMG signal depends on the bulk of muscle in proximity to the recording electrode, the conductivity and geometry of the tissue in the region around the muscle and the recording electrode, and the resistance of the electrode and its contact with the tissue. The most reliable way to standardize the EMG amplitude should be by reference to the EMG generated in a maximal contraction of that muscle. This technique has been used by some authors studying COPD patients (13,14). One drawback is a concern about contamination of the EMG of interest by signals from nearby muscles that might easily be activated in a maximal maneuver. If this did occur, it would result in the normalized EMGs being an underestimate of the true value. A further, hypothetical concern is that the maximum ability of the respiratory control system to activate the muscles might be different from the maximum ability of the voluntary system to do so, i.e., that the voluntary system might have connections permitting more (or less) complete activation of respiratory lower motoneurons than the automatic respiratory controller. In addition, it is possible that maximal activation of these muscles is limited by inhibitory feedback loops that could themselves be altered in the disease state.

A theoretical problem with using quantitative electromyography to estimate the output of the respiratory controller is that the method at its best gives only the motor output to one muscle, usually the diaphragm. To infer overall output of the controller, it is necessary to make the assumption that output to all the respiratory muscles increases by the same percentage as the output to the diaphragm (or a related assumption, such as that each muscle has its output increased in proportion to the diaphragm but in some weighted fashion, for example according to its mechanical advantage). In fact, there are reasons to suppose that other muscles, recruited later, increase their fractional contribution to total output as the output increases. Diaphragm EMG might then underestimate total output as output increases.

Integrated EMG can reliably measure changes in output in one subject through a period of observation or experiment when the same recording electrodes are used throughout. Subject to the reservations about standardization, they are the most accurate way currently available to estimate respiratory motoneuron output in patients.

### *Pattern of Motor Output*

A nonquantitative, but convincing estimate of overall intensity of respiratory motor output can be drawn from the pattern of inspiratory muscle use. Introduced by Galen and used as the foundation for his classification of dyspnea (15), this

method depends on the recognition that inspiratory muscles are recruited in a stereotyped sequence as respiratory motor output increases. At first there are only the diaphragm and clinically imperceptible efforts by parasternal and scalene muscles, then more obvious efforts by scalenes and inspiratory intercostals, then abdominal expiratory muscles, sternocleidomastoids, and finally the superior segment of the trapezius. Occasionally, in severe COPD in extremis, rhythmic inspiratory protrusion of the tongue can be appreciated. No matter what the quantitative measures show, these commonplace clinical observations attest that respiratory motor output is indeed very high in COPD in ARF.

### *Work Rate and Oxygen Consumption of Respiratory Muscles*

Respiratory work rate has also been used in the past as a load-independent measure of respiratory motor output. The work done on the lungs or on the lungs plus chest wall is calculated according to the laws of thermodynamics from pressure-volume loops of the respiratory cycle. Inspiratory work alone or inspiratory plus expiratory work can be used. An important theoretical difficulty is that work, as defined in thermodynamics by area on a pressure-volume diagram ($\int PdV$), is not expected to have a constant or predictable relation to motoneuron discharge. The work done by a muscle contracting in response to a given electrical stimulus is given by the integral of the amount of shortening multiplied by the force it applies to the load it contracts against. An isometric contraction produces no work; neither does rapid shortening without tension. As the configuration of the chest wall and the impedance of the respiratory system change in disease, the amount of work produced by a given motor output is bound to change. A practical problem with the method is that it requires knowledge of the passive pressure-volume curve of the chest wall, which is very difficult to obtain.

Oxygen consumption of the respiratory muscles has also been used as an estimate of output. It is technically very difficult to measure, with rather different results reported by various authors. Also, like work rate, oxygen consumption of a muscle for a given stimulus varies according to the circumstances of contraction of the muscle.

### *The Problem of Nonchemoreceptor Feedback Loops*

As indicated in Figure 4, even a complete and accurate measurement of lower motoneuron activity can give a very distorted picture of intrinsic respiratory center activity, because there are many feedback loops from muscles, upper airways, lungs, and elsewhere that can modify output of the respiratory center itself or of the spinal motoneurons for respiration. Alterations in the traffic in these loops in COPD in acute respiratory failure could make a major difference to measured EMG, and therefore to pressure and ventilation, even if chemoreceptors and respiratory center are operating normally. The nonchemical feedback loops will be discussed below in more detail.

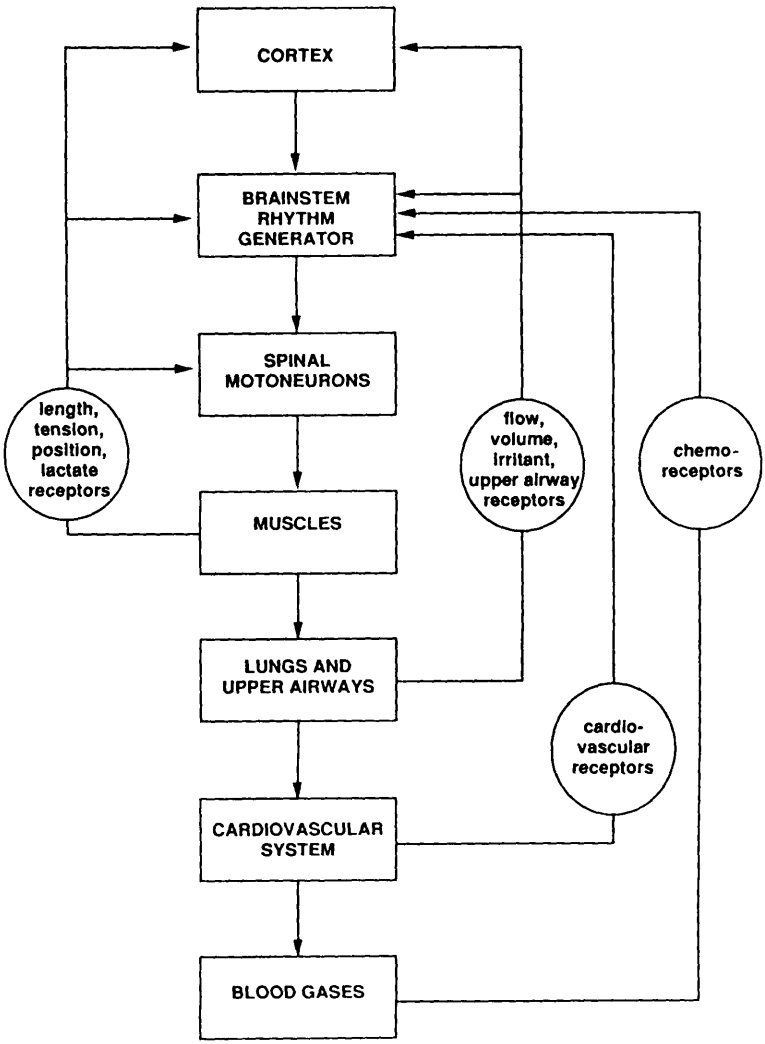



**Figure 4** Diagram of the major feedback loops for respiratory control.

### *Tidal Volume Versus Frequency*

In normal subjects, as ventilation is increased by stimulation with carbon dioxide or exercise, tidal volume and frequency both increase in a predictable way that is the same for both kinds of stimuli. The relation is slightly different if ventilation is stimulated by hypoxia or by raising body temperature, both of which tend to give

higher frequencies and lower tidal volumes than does $CO_2$ for the same ventilation. In normal subjects, these variations in pattern of ventilation have little consequence for gas exchange. By contrast, because of a high $V_D/V_T$ ratio, the $Paco_2$ of COPD patients is rather sensitive to a shift from larger tidal volume and lower frequency to smaller tidal volume and higher frequency. Tidal volume–frequency partitioning of ventilation must therefore be taken into account. When evaluating the output of the controller, normal or pathological factors controlling respiratory rate can play a key role in COPD in acute respiratory failure. Mechanisms determining the partitioning of minute ventilation between tidal volume and frequency are then very important components of the control system output.

#### *Active Adjustments to End-Expiratory Volume and to Volume Profile*

Measurements of minute ventilation, pressure waves, and EMG usually do not and cannot give information about any component of respiratory controller output that acts to apply constant bias to lung volume. Such a bias may be expiratory, keeping end-expiratory volume below relaxed FRC, or inspiratory, keeping end-expiratory volume above FRC. Inspiratory bias implies that inspiratory muscles maintain some activity throughout the respiratory cycle. The tonic component of respiratory motor output is not accounted for in measurements of work, ventilation, or pressure swings, but could constitute an important demand on the muscles. Inspiratory activity in early expiration, which modifies expiratory flow patterns but not tidal volume or frequency, is another component of output that expends energy but is not included in usual measurements of global output. Abdominal expiratory muscles may have as their principal effect an adjustment in configuration of the chest wall, promoting more effective use of the diaphragm (16).

### E. Ventilation-Metabolism Relations—The Metabolic Curve

In any steady-state condition, the obligatory relation between $Paco_2$ and minute ventilation is given by the equation:

$$Paco_2 = K \cdot \dot{V}co_2/\dot{V}_A$$
$$= K \cdot \dot{V}co_2/\dot{V}_E(1 - V_D/V_T)$$

For any given deadspace and $CO_2$ production, this equation describes a hyperbola on the $Paco_2$-$\dot{V}_E$ plot (Fig. 5) called the metabolic curve. Different curves result if $CO_2$ production increases (Fig. 5a) or deadspace to tidal volume ratio increases (Fig. 5b).

In COPD not in acute failure breathing air, values of $V_D/V_T$ range from 0.30 to 0.67 (17), and in a large population study (18) $V_D/V_T$ was $0.486 \pm 0.079$ in normocapnic patients, $0.552 \pm 0.090$ in patients with moderate hypercapnia, and $0.613 \pm 0.070$ in patients with $Pco_2 > 55$. In acute respiratory failure, similar or even higher values have been measured (19) (Table 2). As $V_D/V_T$ increases, the

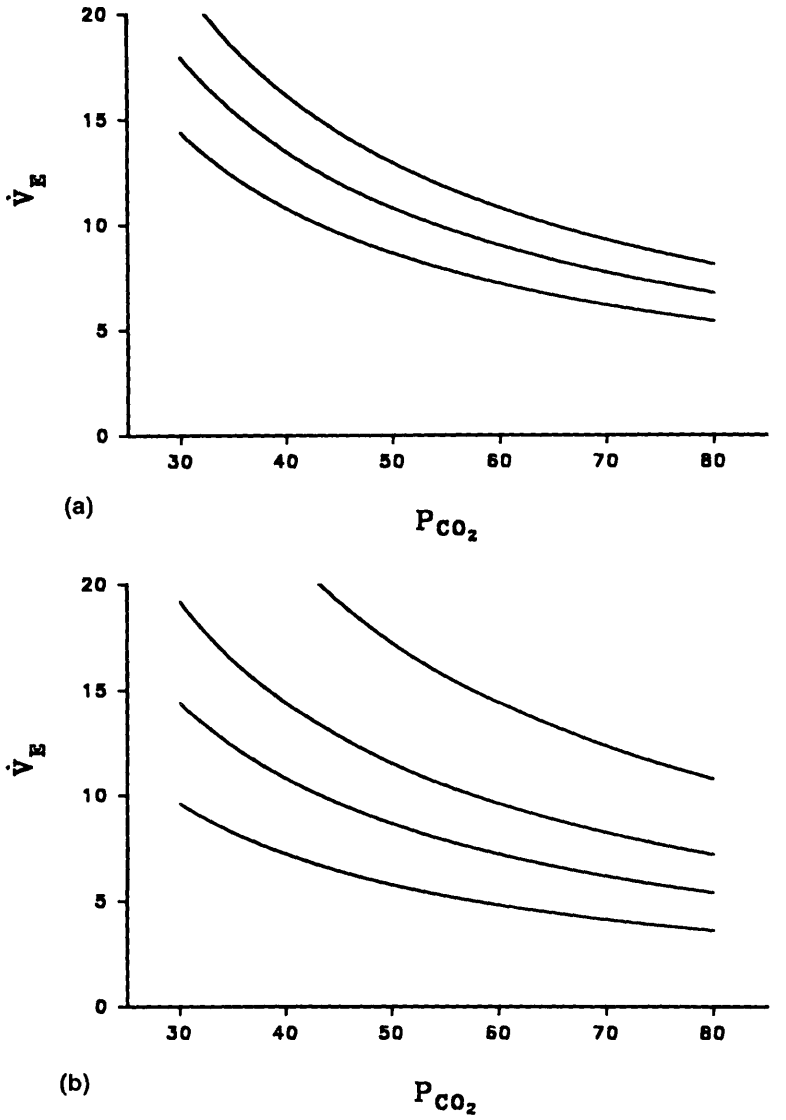



**Figure 5** Typical metabolic curves describing steady-state relationships between arterial $P_{CO_2}$ and minute ventilation. (a) Metabolic curves for different values of $\dot{V}_{CO_2}$ (200 and 300 ml/min from lowest to highest curve). In all cases $V_D/V_T = 0.40$. (b) Metabolic curves for different values of $V_D/V_T$ (0.4, 0.6, 0.7, 0.8, from lowest to highest curve). In all cases, $\dot{V}_{CO_2}$ = 200 ml/min.

**Table 2** Values for Gas Exchange Variables in COPD Patients at Rest

| Ref. Source | $P_{CO_2}$ (mmHg) | $\dot{V}_E$ (L/min) | $V_T$ (L) | F ($min^{-1}$) | $V_D/V_T$ | $\dot{V}_{CO_2}$ (L/min) | $FEV_1$ |
|---|---|---|---|---|---|---|---|
| | | | *Chronic Stable Patients* | | | | |
| 283 | 47 | 9.9 | 0.47 | 21 | 0.43 | 0.37 | 0.37 |
| 17 | 55 | | | | 0.54 | | 40% |
| 284 | 37 | | | | 0.45 | | 0.49 |
| | 55 | | | | 0.55 | | 0.44 |
| 264 | | 9.5 | 0.57 | 17 | 0.63 | 0.20 | |
| 259 | 46 | 13.5 | 0.85 | 17 | 0.49 | 0.28 | 32% |
| | | | | | | | 0.39 |
| 215 | 38 | 10.6 | 0.71 | 15 | 0.52 | 0.26 | 38% |
| | 50 | 9.4 | 0.56 | 17 | 0.57 | 0.28 | 22% |
| 18 | 38 | 10.5 | 0.64 | 17 | 0.49 | 0.271 | 1.73 |
| | 46 | 10.5 | 0.63 | 17 | 0.55 | 0.274 | 1.13 |
| | 62 | 9.1 | 0.56 | 17 | 0.61 | 0.291 | 0.79 |
| | | | *Acute Failure* | | | | |
| 95 | 65 | 10.2 | 0.34 | 32 | 0.77 | 0.21 | |

Where there are two lines of data for the same reference, the upper line refers to normocapnic patients, the lower line to hypercapnic patients. For Begin 1991, the three lines are for normocapnic patients and those with $P_{CO_2}$ between and above - mmHg. The $FEV_1$ values are reported in different format by different authors. 40% means 40% of the predicted values; 0.37 refers to the ratio $FEV_1/VC$; the data of Ref. 18. are reported in liters.

metabolic curve is shifted upward and to the right, as shown in Figure 5b. An important consequence of this is that for any given starting value of $P_{CO_2}$ a certain change in minute ventilation will lead to a greater change in $P_{CO_2}$ in patients with COPD than in normal subjects, as illustrated by the slopes of the lines shown in Figure 5b. (See also Section IXA.)

### F. $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ Gas Transport and Metabolism

Gas transport in the blood and metabolism have been little studied in COPD. Some basic principles with applications in acute failure are reviewed.

In a steady state, carbon dioxide production and transport are equal.

$$\dot{V}_{CO_2} = Q\,(C_{vCO_2} - C_{aCO_2})$$

$$\dot{V}_{CO_2} = \dot{V}_{O_2} \cdot R$$

Normally, $\dot{V}_{CO_2}$ is determined simply by the metabolic demands of the organs for oxygen and by the respiratory quotient, which depends on the substrates

available for metabolism. The respiratory pump, lung gas exchange, and circulatory system provide all the oxygen to tissues that is required. When cardiac output is constrained, or ventilation and gas exchange are inadequate to maintain normal arterial gas tensions, or anemia limits oxygen content of blood, adjustments to the circulatory system and the ability of organs to extract more than the usual amount of oxygen from their arterial supply are sufficient mechanisms to ensure the demands of organ or tissue for oxygen are met. It is quite possible, nevertheless, for the available compensating mechanisms to be overwhelmed by severe, multiple problems in the gas transport system. In that case, the supply of oxygen to tissues may not match the demand. This situation has been described in patients with sepsis, although the validity of these observations is still under discussion (20). In COPD in ARF, especially in patients with concomitant heart disease where there are multiple defects in the gas transport system, the same situation might also occur, but this is not clearly established.

Variations in the respiratory quotient R also have an effect that is well described in COPD patients (21). If R is low, less $CO_2$ is evolved for a given oxygen consumption. When alveolar ventilation is fixed, as in a patient on controlled mechanical ventilation or a patient with limited ventilatory reserve, a diet high in carbohydrates, which gives rise to an R value near 1.0, results in a higher arterial $P_{CO_2}$ than a diet high in fat. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are also increased in febrile patients and can be reduced by cooling (22).

## IV. Classical Analysis of Chemical Control of Breathing

### A. General Concepts

The theory of control of ventilation based on negative feedback from chemoreceptors was one of the first approaches to understanding respiratory failure and still forms a useful starting point for thinking, even though it suffers from numerous difficulties.

The model for a chemoreceptor-based negative feedback system is defined by the diagram in Figure 6. The purpose of the system in its simplest form is to maintain arterial $P_{CO_2}$ close to a normal value. $P_{aCO_2}$ is measured by a chemoreceptor, and this information is fed back to the control center where it is, in effect, compared with a reference value. Any difference between the measured value and the reference value is called an error signal. The error signal is sent to the respiratory pump and causes it to change its ventilation in a way that tends to bring $P_{aCO_2}$ back toward the reference value. The control system is said to be very sensitive if a small deviation of $P_{aCO_2}$ from the reference value causes a large adjustment in ventilation. In that case, only small deviations from normal $P_{aCO_2}$ are allowed to occur. The sensitivity of the control system is assessed by forcing a change in $P_{aCO_2}$ and measuring the resulting change in ventilation. The function

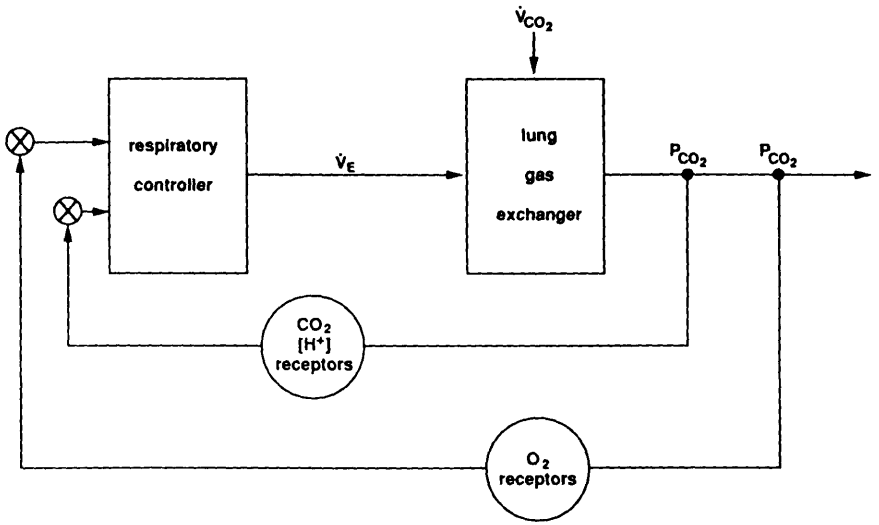



**Figure 6** Block diagram describing the feedback system for control of blood gases depending on chemoreceptors.

that describes the ventilation for any given value of $Paco_2$ is called the "controller curve," and the sensitivity of the controller is given by the slope of the $e\dot{V}$-$Paco_2$ curve at the operating point. Extensive work in normal subjects has defined controller curves for various conditions. In most experiments the $\dot{V}$-$Paco_2$ relationship can be well described by a straight line, characterized by a slope and an intercept (23). There is a wide range of values for this slope in normal subjects and in COPD patients. The slope can be modified by many factors, including the cerebral cortex (24), whether the eyes are open or closed (25), and the sleep state.

Chemoreceptors are sensitive to $Pao_2$ and pH as well as to $Pco_2$. Ventilatory responses to these other inputs can be described by themselves under the condition that $Pco_2$ is held constant. The characteristics of the normal complete chemoreceptor feedback system are described by experiments in which ventilatory response to $Pco_2$ is measured at several different levels of $Po_2$ (26,27) or several different levels of pH (28). These data show that hypoxemia progressively increases the slope of the $\dot{V}$-$Paco_2$ relationship (Fig. 7a). It is approximately true that the intercept of the relation at zero ventilation is not changed by hypoxemia, but points on the controller curve in the region of normal resting ventilation for a hypoxemic subject are to the left of the controller curve for a nonhypoxemic subject. When pH is changed by infusion of acidifying or alkalinizing agents,

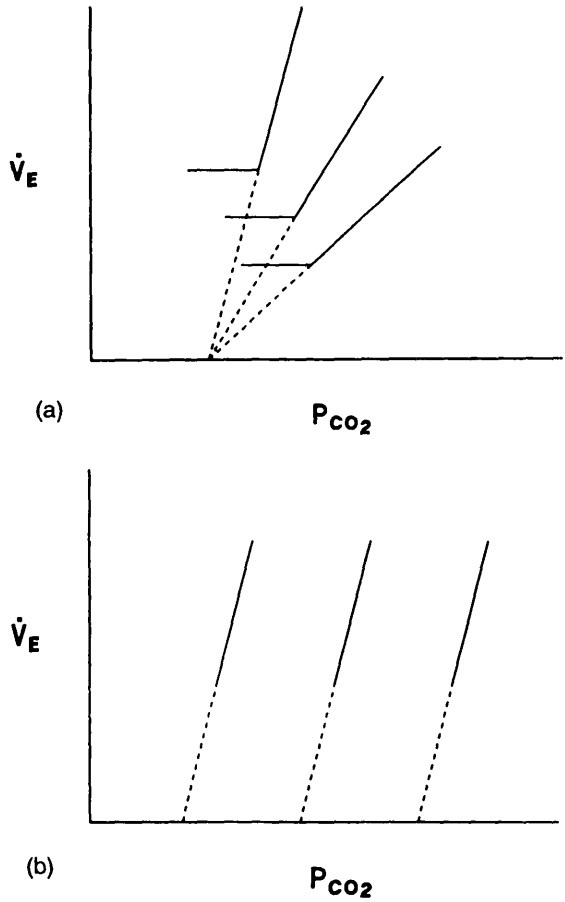



**Figure 7** (a) Ventilatory response curves to carbon dioxide at three different levels of oxygen: lowest curve for hyperoxia, highest curve for hypoxia. (b) Ventilatory response curves to $CO_2$ at three different levels of bicarbonate: leftmost curve, metabolic acidosis; rightmost curve, metabolic alkalosis.

$\dot{V}_E/P_{CO_2}$ controller curves are shifted to right or left without much change in slope (28) (Fig. 7b). The two families of response curves describe the interaction between the three major stimuli to respiratory chemoreceptors.

In a steady state, the $P_{aCO_2}$ and $\dot{V}_E$ values for a subject must fit on the metabolic curve and at the same time should describe the position of a point on some controller curve. The slope of the controller curve can be measured, as above, and the curve drawn on the $P_{aCO_2}$-$\dot{V}_E$ plot (Fig. 8a). Because both equations

must be satisfied, the only possible values of $P_{CO_2}$ and $\dot{V}_E$ in a steady state are the ones corresponding to point A, at the intersection of the two curves.

In a pure negative feedback control system, these two equations (the metabolic curve and the controller curve) should predict the behavior of the system when $\dot{V}_{CO_2}$ or deadspace is changed. For example, if deadspace increases, the subject must move to a new steady state at B on the new metabolic curve. The increase in deadspace causes an increase in $P_{aCO_2}$, which in turn causes an increase in ventilation. The amount of increase in ventilation is determined by the slope of the controller curve. If it is steep, there is a large increase in ventilation and only a small increase in $P_{aCO_2}$ (point C). On the other hand, if the chemoreceptor system is insensitive, defined by a small slope of the controller curve, ventilation increases only slightly, and $P_{aCO_2}$ rises much higher (point D).

When this analysis in its simple form is applied to any subject with an abnormally high $P_{aCO_2}$, it leads to the conclusion that there is a fault in the control system resulting in an abnormal controller curve (Fig. 8b). The abnormality might be a shift to the right due to metabolic alkalosis (dashed line in Fig. 8b) or a decrease in slope (dotted line in Fig. 8b) due to damage or inhibition of chemoreceptors or to mechanical hindrance to ventilation.

### B. Limits to Validity of the Chemoreceptor Negative Feedback Control Theory

There are no physiological situations that correspond exactly to the experiment of increasing $P_{CO_2}$ by increasing the concentration of $CO_2$ in the inspired gas, which is the method used to define the chemoreceptor controller curves. When negative feedback theory is tested in two key physiological conditions that correspond to disorders that may be found in COPD, the results are not as predicted.

One condition is the increase in $\dot{V}_{CO_2}$ that can be seen in exercise or in hyperthyroidism. The exercising subject has high ventilation at normal or below-normal $CO_2$. This implies that the "controller curve" has shifted upward or to the left. The response to changing $P_{CO_2}$ can still be defined by inhaling gas with increased concentrations of $CO_2$, and the slope of the shifted control curve can be determined, but the explanation of exercise hyperpnea lies outside the theory of negative chemoreceptor feedback defined by this slope. Other control mechanisms must be looked for. Some of these are classified as "feed-forward" systems, in which ventilation increases in direct response to an increase in $\dot{V}_{CO_2}$ or $\dot{V}_{O_2}$. An extensive literature exists with regard to mechanisms that are proposed to explain exercise hyperpnea (29–32). These include input from such correlates of exercise $\dot{V}_{CO_2}$ as intensity of motor command to exercising muscles, or cardiac output, or respiratory fluctuations in $P_{aO_2}$ at arterial chemoreceptors, or afferents from exercising muscles. At present, there are no good methods to quantify the effectiveness of feed-forward control mechanisms, or to perceive the extent to which they might be operating in COPD.

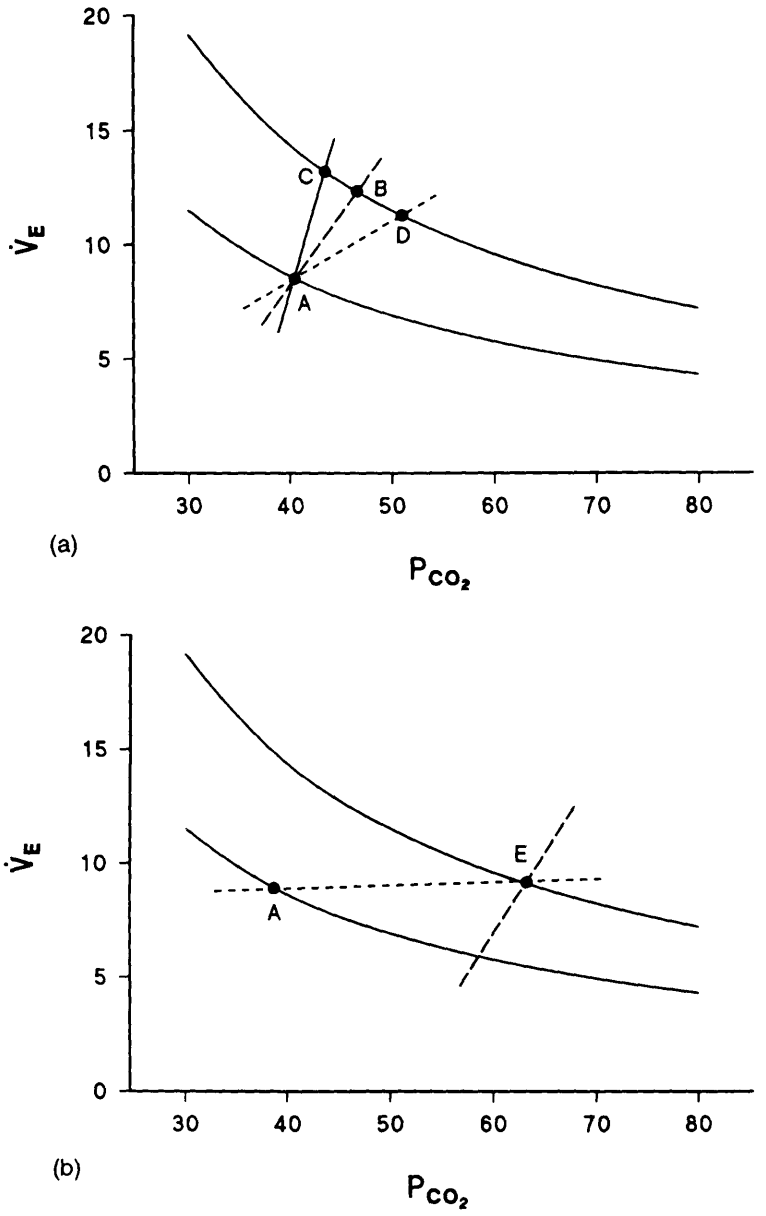



**Figure 8** Prediction of behavior of a ventilatory control system depending on negative feedback from chemoreceptors. (For explanation see text.)

There is much less literature about the effect on ventilation of an increase in deadspace, but the data we have suggest that ventilation increases more in response to added deadspace than is predicted by the ventilatory response to inhaled carbon dioxide (33–35). It appears, therefore, that an external deadspace can stimulate ventilation in other ways than by raising mean level of arterial $P_{CO_2}$, perhaps through respiratory fluctuations in arterial $P_{CO_2}$ or $P_{O_2}$.

There are questions about the slope of the ventilatory response curve at the actual operating point. The slope is almost always measured in a range of $P_{CO_2}$ higher than the operating point, where it has the familiar form of a line with constant slope. When $P_{CO_2}$ is driven below the operating point in conscious subjects, however, ventilation does not decrease, but remains nearly constant at a level not much different from normal resting conditions, so that the complete curve of ventilatory response to $CO_2$ takes the form of a "hockey stick," with a bend near the operating point (see Fig. 7a). The sensitivity to $CO_2$ that is important for minute-to-minute regulation probably corresponds to the slope somewhere near the bend in the curve and may be much less than the steep slope measured at higher levels of $P_{CO_2}$.

These and other issues about interpretation of $CO_2$ response curves are reviewed elsewhere (36–39).

### C. Limits to Ventilation and Nonlinearity of the Ventilation Response Curve to $CO_2$ at High $CO_2$

In experiments on normal subjects stimulated with $CO_2$ the ventilation response to $CO_2$ is conveniently approximated as a straight line. It is evident, however, that no such response curve can continue as a straight line to indefinitely high levels of ventilation. There must be, for every person, a maximum sustainable level of ventilation. The maximum may be determined purely by mechanics, particularly by the maximum expiratory flow volume curve, which puts a strict limit on ventilation. Or it may be determined by the maximum capacity of respiratory muscles to sustain the work required for ventilation. (The details of these possibilities are discussed in Chapter 5.) Or it may be determined in some cases by some other overriding factor, such as pain, dyspnea, or feedback from pulmonary or muscle receptors.

In any case, when the patient's ventilation approaches the maximum sustainable level, the $CO_2$ response curve must stop being linear. It could curve to make an asymptote with the maximal sustainable level, or it could continue in a straight line until the maximum is reached abruptly. For the sake of argument, we can assume the response curve near the maximum sustainable ventilation approaches a plateau as shown in Figure 9. In a well-designed control system, the plateau would be somewhat below the maximum sustainable level, to leave a safety margin. If the system were to move above a maximum sustainable level

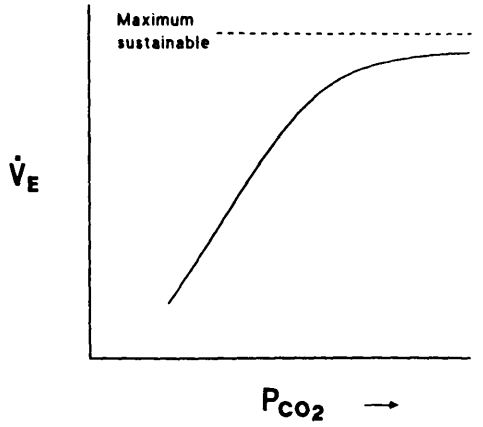



**Figure 9** Hypothetical ventilatory response to $CO_2$. (For explanation see text.)

determined by muscle capacity, for example, it would immediately begin to develop fatigue and this would result in an unstable state.

It is reasonable to suppose that some patients in acute respiratory failure due to COPD are approaching maximal sustainable ventilation and therefore are in a region of the ventilatory response curve that is much flatter than the region that is assessed when the patient is well. Depending on the shape of the response curve, small changes in $P_{CO_2}$ or ventilation could move the operating point enough to make a substantial difference in the slope of the curve and thus in the operating characteristics of the $P_{CO_2}$-$\dot{V}_E$ controller.

### D. Adaptations of the Control System to Sustained Blood Gas Abnormalities

It is not unreasonable to expect that the control systems of patients with COPD might be modified as a result of operating over days, weeks, or months in abnormal conditions. In particular, days, weeks, or months with high carbon dioxide and low oxygen may cause alterations in the response of the system to chemical stimuli. Known possible central and peripheral mechanisms for such alterations are very complex and have been critically reviewed by Dempsey and Forster (37) and Lahiri and Gelfand (40).

#### *Sustained Hypoxemia*

Patients with chronic hypoxemia seem to have a definite decrease in chemosensitivity to hypoxemia. The mechanism for this is not known, but the behavior of COPD patients in this respect (41) is parallel to that of other patients with chronic

hypoxemia who develop a reduction in sensitivity to hypoxemia, namely patients with cyanotic congenital heart disease (42,43), patients with sleep apnea (44,45), and high-altitude dwellers (reviewed in Ref. 46). In COPD, the defect is not reversed by treatment with oxygen (47). Naloxone does improve the ventilatory response to hypoxia in COPD (48) but not in normal subjects (49), suggesting that endogenous opioids play a role in the depression of the response in COPD.

In addition to the effect of a prolonged exposure to hypoxemia on ventilatory response to hypoxemia, there are two shorter-term adaptations that should eventually be considered in evaluating the effect of hypoxia on control of breathing in ARF. One is the attenuation of ventilatory response to hypoxia seen in normal subjects who are given a 30-min square wave of isocapnic hypoxia (50). The initial increase in ventilation falls off to a third or less after 20 min of sustained hypoxia, and this slow-onset inhibition takes many minutes to wear off (51), which suggests it is mediated by an increase in brainstem levels of some neurotransmitter. γ-aminobutyric acid (GABA) adenosine (288) (52,53) and dopaminergic mechanisms (54) have been implicated. Rapid progressive hypoxic stimulation tests may thus overestimate the real functional sensitivity to hypoxemia. Second, normal subjects going to high altitudes show a progressive increase in sensitivity to hypoxemia over several days, as part of acclimatization (reviewed in Ref. 46). Whether this happens in COPD patients made acutely hypoxic for a few days has not been investigated.

### *Sustained Hypercapnia*

There is less evidence about adaptations to sustained abnormalities in blood $CO_2$ levels, and it is hard to identify the effects of sustained hypercapnia alone because it usually occurs in conjunction with hypoxemia, but several pieces of evidence suggest that sustained hypercapnia can indeed change the control system.

Direct experimental evidence came from studies in which normal men were kept for many days in an atmosphere enriched in $CO_2$. Initially Schaeffer (55) kept two volunteers in 3% $CO_2$ in air for 2–4 days and found a decrease in ventilatory response to $CO_2$. In a larger study (56), 21 volunteers stayed in an atmosphere of air with $P_{CO_2}$ = 10.5 mmHg for 42 days. They showed a progressive increase in minute ventilation: 10–20% on the first day, and a further increase of 15% by day 5. After that, minute ventilation remained constant, but for another 2 weeks there was a progressive increase in alveolar ventilation through reduction in deadspace and adjustment of tidal volume and frequency. By the end of the exposure period there was a small reduction in ventilatory response to $P_{CO_2}$. In another study (57), ventilatory response to $CO_2$ was still normal after 5 days in an atmosphere with $P_{CO_2}$ 30. The rise in arterial $P_{CO_2}$ induced by these exposures would have been very modest, about 5 mmHg in an atmosphere of $P_{CO_2}$ = 30 mmHg, and much less for $P_{CO_2}$ = 10.5 mmHg. It might be expected that COPD patients with larger

increments in $P_{CO_2}$ over longer periods might have larger adjustments in their control systems than the volunteers in these simulated submarine accidents.

In the opposite direction, when $P_{CO_2}$ was lowered in patients with partial respiratory muscle paralysis by overventilating them in an iron lung and the iron lung was turned off after many hours of overventilation, the patients continued to hyperventilate for some hours, maintaining a respiratory alkalosis by maintaining the same high ventilation, but now at a lower $P_{CO_2}$. Both the hypocapnia and the ventilation volume seemed to act as stimuli (58,59).

During acclimatization to altitude, sustained respiratory alkalosis with hypoxemia is associated with an increase in ventilatory response to $CO_2$ that seems to be due to adaptive changes in the carotid body (reviewed in Ref. 46). Patients who have been hypoxic or hypoxic and hypercapnic intermittently at night because of obstructive sleep apnea can eventually develop daytime hypercapnia and may then have reduced ventilatory sensitivity to $CO_2$ (tested in the awake state, when they have no mechanical hindrance to breathing), which returns toward normal when their sleep apnea is treated (60,61). Other authors report that the slope of the ventilatory response to $CO_2$ is not much changed but the curve shifts to the left with treatment over many weeks (44,62).

The increased buffering capacity of blood and interstitial fluid that is present in compensated respiratory acidosis might be expected to cause a reduction in the slope of the ventilatory response to $CO_2$ because the proximate stimulus to chemoreceptors is thought to be hydrogen ion concentration ($[H^+]$) rather than $CO_2$ itself. The site of the receptors, particularly along the gradient in $[H^+]$ from arterial to venous, and the importance of the contributions of stimuli from peripheral versus central receptors remain unclear. Theoretical calculations of the effect of chronic elevation in $[HCO_3^-]$ on ventilatory response to $CO_2$ must therefore be viewed as speculative. Flenley and Millar (63) did such calculations, assuming the main effect was through buffering in arterial blood, and found that the calculated effect of buffers would explain only a small part of the reduction in ventilatory response observed in their patients. In a further experiment (64), they measured CSF bicarbonate as well as ventilatory responses to $CO_2$ in 12 COPD patients and again found that buffering could not explain the reduction in slopes of the ventilatory response. On an experimental level, Fishman et al. (65) changed bicarbonate levels in COPD patients by giving acetazolamide over several days and found no measurable changes in ventilatory response to $CO_2$.

Another mechanism for effect of sustained hypercapnia on control of breathing is suggested from experiments that argue that several different stimuli that increase resting ventilation also increase ventilatory response to exercise and show that for one of these stimuli, an added deadspace in awake goats, this "short-term modulation" of ventilatory response can be eliminated by giving methysergide (66). The authors hypothesize that facilitatory serotonergic neurons in the brainstem raphe are responsible for the change in exercise ventilation. Repeated

2-min challenges of 5% $CO_2$ breathing in normal men can cause short-term modulation of the respiratory response, such that toward the end of a series of six challenges, while the increase in ventilation is the same, it is achieved by relatively larger tidal volumes with lower frequency and higher mean inspiratory flow (67). Even a single breath of $CO_2$-enriched air in humans induces a prolonged increase in ventilation (68). A different kind of adaptation was observed in another experiment with goats exercised repeatedly on a treadmill (69). When the goats performed each session of exercise with an added deadspace so that their arterial $P_{CO_2}$ was higher than normal during exercise, they gradually altered their ventilatory response so that after many exercise sessions they were found to have a higher resting ventilation and a steeper ventilatory response to $CO_2$ than before (termed "long-term modulation" by the authors). The demonstration of this kind of 'learning' of a ventilatory response after multiple exposures to a certain situation raises the fascinating possibility that many observed ventilatory behaviors are the result of learning from previous experience rather than depending on contemporaneous feedback.

If some of the ventilatory control abnormality in COPD can be attributed to the high $CO_2$ itself, this begs the question of how the $CO_2$ came to be high in the first place. One postulate is that blood gases could be more severely disturbed in sleep, and that prolonged nocturnal hypoxemia and hypercapnia could lead to chronic adaptations of the respiratory control stem as seems to occur in obstructive sleep apnea, where severe upper airway obstruction at night eventually results in chronic daytime hypercapnia. Another is that repeated rises of $CO_2$ during exercise might have an effect over time.

The multiple effects of hypercapnia on the circulation, nervous system, endocrine system, lungs, gut, and kidneys have been reviewed recently (70) with the conclusion that few harmful effects are to be expected in mechanically ventilated patients if the $P_{CO_2}$ does not go beyond 80 or the pH below 7.15, assuming oxygenation is assured and there are not other complicating medical problems.

### E. Ventilatory Response to $CO_2$

#### *Chronic Stable COPD*

As long ago as 1920, Scott (71) demonstrated that patients with emphysema had a less than normal increase in ventilation upon inhaling a gas mixture containing carbon dioxide. After the introduction of arterial blood gas measurement, it was found that many patients with advanced COPD had above-normal resting values of arterial $P_{CO_2}$. Since then, numerous investigations have been performed in attempts to answer the general question whether the decreased sensitivity to changes in $P_{CO_2}$ and the abnormal resting level of $CO_2$ are primarily due to a disorder of control of breathing (the "won't breathe" hypothesis) or simply to

limitations on ventilation imposed by lung and chest wall mechanics (the "can't breathe" hypothesis). One kind of investigation tries to assess response to changes in $CO_2$ by a method that is not confused by purely mechanical limitations to ventilation. The other kind is a population study that seeks correlations between resting $CO_2$ and measurements of mechanics, or muscles, or pattern of breathing (see Section XA).

Scott's initial observation (71) was confirmed by Meakins and Davies (72), and it was found (72,74) that the degree of depression of ventilatory responsiveness to $CO_2$ was correlated with the resting value of $P_{CO_2}$. The first extensive study to take mechanics into account (75) measured resting ventilation and $P_{CO_2}$, response to 100% oxygen, and steady-state responses to $CO_2$ in hyperoxia in 35 dyspneic, emphysematous subjects and 13 control subjects. Respiratory function was assessed by mixing efficiency, vital capacity, RV/TLC (by helium dilution), and maximum breathing capacity. For the patients, mean ventilatory response to $CO_2$ ($\Delta \dot{V}_E/\Delta P_{CO_2}$ in L/min/mmHg) was 0.91 compared to 2.15 for controls. There was a loose, inverse correlation between ventilatory response to $CO_2$ and the resting arterial $P_{CO_2}$. Maximum breathing capacity also correlated directly with ventilatory response to $CO_2$ and inversely with resting $P_{CO_2}$, but this estimate of the muscle/mechanical limits of the respiratory pump accounted for only a small part of the variance in resting $P_{CO_2}$ or in response to $CO_2$.

The point of view that reduced sensitivity to $CO_2$ was the problem rather than a mechanical limitation was supported by Fishman et al. (65), who found patients with hypercapnia had a lower ventilatory response to $CO_2$ than those with normocapnia but could nevertheless increase their ventilation during exercise, and by Alexander et al. (76), who found some patients with severe mechanical limitation but normal ventilatory responses.

The first attempt to evaluate sensitivity of the respiratory centers in COPD using a method of measuring respiratory center output supposed to be independent of lung mechanics was made by Richards et al. (77), using oxygen consumption. They found the $\dot{V}_{O_2}$ response to $CO_2$ in COPD patients was normal and concluded that the sensitivity of the respiratory centers was normal, and the reduced ventilatory response was therefore due to a mechanical limitation. The difficulty of the methods, the small numbers of patients, and the many assumptions necessary in the interpretation of results made this approach unconvincing. Cherniack's group reassessed this concept using both work of breathing and oxygen consumption of respiratory muscles. They showed that addition of a resistive load to normal subjects decreased their ventilatory response to $CO_2$ (78) and increased the work rate response to $CO_2$ (79). COPD patients had below-normal work rate responses to $CO_2$ and 4–5 times normal respiratory muscle oxygen consumption responses to $CO_2$ (80). If the respiratory muscle oxygen consumption is taken as the best measurement of respiratory output, the conclusion is that the respiratory center sensitivity was above normal, but if work of breathing is chosen, output was below

normal. Flenley and Millar (81) found that COPD patients had nearly double the work of breathing per unit of minute ventilation as normals, but nevertheless had lower-than-normal rates of increase in work of breathing with $CO_2$ stimulation and concluded that decreased respiratory center sensitivity to $CO_2$ was an important factor.

Quantitative electromyography of the diaphragm was first applied to the problem by Lourenço and Miranda (82), who measured diaphragm EMG ($E_{di}$) response to $CO_2$ in nine normal subjects, five COPD patients with normal resting $P_{CO_2}$, and eight COPD patients with $P_{CO_2}$ above 56. The normocapnic patients had slightly above normal EMG responses, whereas the hypercapnic patients had responses averaging 10% of normal. Their method for standardizing the EMG was not clearly spelled out. More recently, Scano et al. (83), using $E_{di}$ expressed as the rate of rise in inspiration normalized to the EMG during an inspiratory capacity maneuver, compared nine normal subjects with nine normocapnic COPD patients and found the EMG response to $CO_2$ in the patients was about twice normal.

Occlusion pressure ($P_{0.1}$) in COPD patients breathing through a mouthpiece, assessed by Zackon et al. (84) was above normal at a reference $P_{CO_2}$ of 60, but increased less than normal with increasing $P_{CO_2}$.

Bradley et al. (41) compared 20 chronically hypoxemic patients with 17 normoxemic ones who had similar mechanical impairment judged by lung volumes and $FEV_1$. Hyperoxic ventilatory responses to $CO_2$ were lower in the hypoxemic patients, but $P_{0.1}$ responses were not different. The hypercapnic, hypoxemic patients had similar ventilatory responses but lower $P_{0.1}$ responses than the normocapnic ones. After a group of 30 such hypoxemic COPD patients had been treated for 6 months with home oxygen, 24 hr/day, their resting $P_{CO_2}$ rose from a mean of 43.9 to 48.7 and both their ventilatory and occlusion pressure responses to $CO_2$ in hyperoxia fell (from 0.49 to 0.29 L/min/mm Hg and from 0.40 to 0.14 $cmH_2O$/mmHg, respectively), in spite of there being no measurable changes in mechanics over that period (47). These data clearly suggest that sensitivity of the central controller to $CO_2$ declined over time in these patients in association with the rise in resting $P_{CO_2}$.

Like Flenley and Millar (63), Fahey and Hyde (85) tried to allow for muscle/mechanical limitation by expressing ventilation for each subject as a percentage of the maximum voluntary ventilation. Ventilatory response to $CO_2$ normalized in this way was normal in nine COPD patients with normocapnia, but below normal in 12 with hypercapnia, suggesting that the hypercapnic patients have a primary problem of reduced respiratory center sensitivity to $CO_2$. On the other hand, Gorini et al. (14), in their study of 15 patients, found that $P_{CO_2}$ correlated best with the ratio of normalized diaphragm EMG to occlusion pressure ($P_{0.1}$). They interpreted this ratio as an index of the mechanical effectiveness of respiratory muscle contraction and proposed that the main determinant of ventilation was a loss of effectiveness of the muscles.

An important observation is that COPD patients stimulated with $CO_2$ show much less increase in tidal volume than normals but increase ventilation mainly by increasing breathing frequency (86).

In summary, many studies have shown that the ventilatory response to $CO_2$ is reduced in severe COPD, and that the response is less in patients with hypercapnia than with normocapnia even when the mechanical impairments are equivalent, as far as can be judged by pulmonary function testing (Table 3). Long-term use of oxygen causes a reduction in response and a rise in resting $P_{CO_2}$. Attempts to separate the mechanical/muscle component from the central nervous system component of ventilatory response by measuring output as occlusion pressure, work, oxygen consumption, EMG, or ventilation as percent MVV are not wholly

**Table 3** Slopes of Ventilatory Response Curves in COPD Patients

| Ref. Source | *N* | $\Delta\dot{V}_E/\Delta P_{CO_2}$ | | $\Delta P_{0.1}/\Delta P_{CO_2}$ | $\Delta\dot{E}_E/\Delta Sa_{O_2}$ | $\Delta P_{0.1}/\Delta Sa_{O_2}$ |
|---|---|---|---|---|---|---|
| | | | *Chronic Stable Patients* | | | |
| 75 | 35 | 0.91 | | | | |
| 79 | 10 | 0.77 | (1.7) | | | |
| 63 | 8 | 0.75 | (1.9) | | | |
| 81 | 8 | 0.67 | (1.6) | | | |
| 82 | | 2.0 | (3.7) | | | |
| | | 0.47 | | | | |
| 84 | 10 | 1.0 | (3.2) | 0.55 | −0.21 | −0.30 |
| 41 | 17 | 0.99 | | 0.37 | −0.17 | −0.07 |
| | 20 | 0.54 | | 0.38 | −0.17 | −0.12 |
| 47 | 30 | 0.52 | | | | |
| 85 | 21 | 0.80 | | | | |
| | | 0.55 | | | | |
| 101 | 14 | | | 0.63 | | −0.15 |
| 83 | 9 | 0.88 | | | | |
| 106 | 25 | | | | −0.35 | −0.16 |
| | | | | | −0.28 | −0.24 |
| 98 | 14 | | | | −0.74 | −0.51 |
| | | | *Acute Failure* | | | |
| 19 | | 0.18 | | | | |
| 92 | 6 | 0.11 | | | | |
| 91 | | 0.17 | (1.6) | | | |

*N* refers to the number of patients studied. The units for $\Delta V_E/\Delta P_{CO_2}$ are L/min/mmHg, for $\Delta P_{0.1}\Delta P_{CO_2}$ are $cmH_2O$/mmHg, for $\Delta V_E/\Delta Sa_{O_2}$ are L/min/%, and for $\Delta P_{0.1}/\Delta Sa_{O_2}$ are cmH2O/%. The numbers in parentheses are normal values measured by the same authors with the same techniques as part of their study.

convincing because of the small numbers of patients in each study, the scatter in the results, and the technical and theoretical problems of the various methods. However, most studies suggest that central nervous system sensitivity to $CO_2$ is reduced in many patients, particularly those with chronic hypercapnia, and that there are wide interindividual variations in that sensitivity. Additional, circumstantial evidence in favor of important interindividual differences in $CO_2$ sensitivity in COPD comes from studies of families that show that $CO_2$ responsiveness is partly determined by heredity (87–90).

### *Acute Respiratory Failure*

None of the background data on COPD in a chronic stable state is necessarily applicable to the situation in acute respiratory failure, where the number of direct observations is fewer. There have been three studies that give direct information about ventilatory response to $CO_2$ in patients being treated for acute respiratory failure.

In one study, from the unit of Derenne (19), patients spontaneously breathing air through a mouthpiece on the first day of admission were switched to 100% oxygen. This led to an immediate drop in ventilation due to removal of the hypoxic stimulus, but it was followed by a gradual recovery of ventilation over 10 min that could be attributed to a rise in $CO_2$ (Fig. 10). The data permitted an estimate of ventilatory response to $CO_2$ in hyperoxia of 0.18 L/mmHg.

In a more recent study, Tardif et al. (91) measured ventilatory and $P_{0.1}$ response to $CO_2$ in hyperoxia in 25 COPD patients on the fifth day after admission

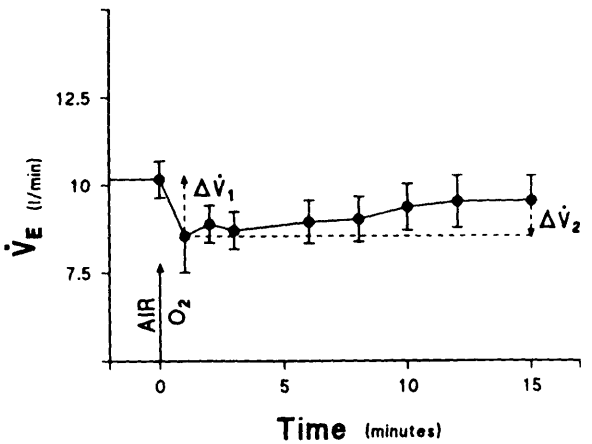



**Figure 10** Effect of administration of 100% oxygen on ventilation in patients with acute respiratory failure. (Modified from Ref. 19.)

for acute respiratory failure requiring mechanical ventilation. By that time, all had been in a nearly steady-state condition for 48 hr with their blood gases close to normal (mean $P_{CO_2}$ 42 mmHg, pH 7.43, bicarbonate 27.4). They were disconnected from the ventilator and allowed to breathe spontaneously for 6–8 min into an 8–10 L bag containing oxygen. (This rebreathing technique was shown to give the same result as a Read rebreathing technique in another set of patients.) In the 25 patients the slope $\Delta\dot{V}_E/\Delta P_{CO_2}$ had a mean of 0.17 L/min/mmHg (10% of the slope for normal controls). The respiratory frequency response to $CO_2$ was 0.34 per mmHg (1.5 times the control value). The tidal volume response was very limited, 2.7 ml/mmHg (5% of the control value). The response of inspiratory flow rate was 8.2 ml/sec/mmHg (15% of the control value). The resting value of $P_{0.1}$ was higher in the patients than in normals at low $CO_2$ but the slope of the occlusion pressure response was only 60% of that for the normals (Fig. 11). If a correction is applied to allow for the recognized decrease in effectiveness of the diaphragm, using data from Similowski et al. (12) in chronic COPD patients tested with artificial stimulation of the phrenic nerve and showing 60% of normal twitch Pdi, the average slope of $P_{0.1}$ is very close to that found in normal subjects. In the same study, Tardif et al. (unpublished results) measured ventilatory responses to $CO_2$ in each subject repeatedly during their stay in the ICU, obtaining up to seven slopes over periods of up to 15 days. The slopes changed somewhat over the first 48 hr

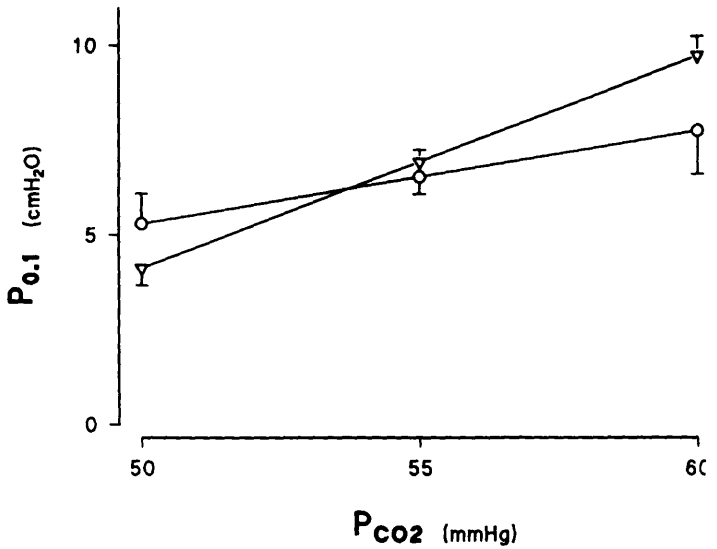



**Figure 11** Occlusion pressure response to $CO_2$ in patients with COPD in ARF (circles) compared to normal subjects (triangles). (Modified from Ref. 91.)

but remained constant after that in each subject. Also important to note is that the mean values for the group conceal major interindividual variations, with slopes of ventilatory responses ranging from 0.06 up to 0.50 L/min/mmHg, and $\Delta P_{0.1}/\Delta P_{CO_2}$ ranging from 0.04 to 1.40 $cmH_2O$/mmHg. The ability to wean patients from the ventilator did not correlate with their ventilatory sensitivity to $CO_2$.

These results are of special importance because the slope of the response to $P_{CO_2}$ was obtained after 2 days of normalized blood gases, so the medium-term effect of low oxygen, high $P_{CO_2}$, and high bicarbonate per se on the controller should have been largely eliminated. In addition, the $P_{0.1}$ values measured through an endotracheal tube are much more reliable than those from other studies where a mouthpiece was used.

In a similar, smaller study Amaha and Sha (92) measured ventilatory response to $CO_2$ in six patients in a stable state, who had been ventilated for many days in an intensive care unit, and found a mean slope of 0.11 L/min/mmHg. Some months later, when they were in a chronic stable state no longer requiring ventilator support, the same patients had a mean slope of 0.30 L/min/mmHg.

Table 3 gives a summary of available measurements of ventilatory and occlusion pressure response to $CO_2$ in COPD patients while in a chronic stable state, with and without hypercapnia, and in acute respiratory failure.

The data leave no doubt that most patients with COPD in acute respiratory failure do respond to $CO_2$ by increasing ventilation and occlusion pressure. Their chromoreceptors therefore remain sensitive to some degree. Tardif et al. (91) calculated that the $CO_2$ stimulus in fact could be responsible for a third of the ventilation noted in their average patient. The slope of the ventilatory response curve is much lower than in the same or similar patients when they are in a chronic stable state. The reasons for this are not certain and remain to be explored (see Section XI). Patients in acute respiratory failure have a wide range of values of pH or $[H^+]$ for the same $P_{CO_2}$, indicating a wide range of degrees of metabolic alkalosis or acidosis (8,19,93–95). Hydrogen ion shifts the ventilatory response curve to right or left but probably has little effect on slope. As found in studies on normal subjects and on stable COPD patients, there continue to be major interindividual differences in sensitivity to $CO_2$, and some patients have no measurable response. It is important to note that, even more so than chronic stable patients, the patients in acute failure increase mainly breathing frequency, with little change in tidal volume.

### F. Ventilatory Response to Hypoxemia

#### *Patients Without Acute Problems*

The interaction between $CO_2$ and $O_2$ on chemoreceptors makes interpretation of chemosensitivity data in COPD patients particularly difficult. The slope of the ventilatory response to oxygen, expressed as $Sa_{O_2}$ or as coefficients of the hyper-

bolic relation between $Pa_{O_2}$ and ventilation, depends on the level of $Pa_{CO_2}$ at which the test is conducted. It could be expected, therefore, that patients with hypercapnia but with normal chemoreceptor mechanisms for oxygen would show steeper slopes of ventilatory responses to hypoxemia than normocapnic subjects. (It is important to note that the $CO_2$-$O_2$ interactions refer to acute elevations of $P_{CO_2}$ associated with corresponding changes in $[H^+]$ of acute respiratory acidosis, and cannot be extended quantitatively to patients with chronic "compensated" respiratory acidosis.) Flenley and Millar (63) evaluated sensitivity to hypoxemia in COPD patients by examining the converse relationship between $O_2$ and $CO_2$: the effect of hypoxemia on the slope of the ventilatory response to $CO_2$. In normal subjects during acute experiments involving breathing of various gas mixtures for 15–20 min each to reach equilibrium, it had been demonstrated by Nielson and Smith (27) and elaborated by Lloyd et al. (26) that slope of the ventilatory response to carbon dioxide depends on the level of oxygen during the test. Flenley and Millar (63) performed these rigorous and demanding tests on five COPD patients. To cancel the effects of mechanics on the ventilatory response slopes and to normalize across subjects, they calculated the ratio of the slopes $\Delta\dot{V}_E/\Delta P_{CO_2}$ in hypoxemia (below 70 mmHg) and hyperoxia (above 120 mmHg) and found it to be indistinguishable from the available data on normal subjects. They were thus unable to detect an abnormality in sensitivity to hypoxemia. In a subsequent trial (64), they performed the same procedure on 12 patients and found two of them (the ones with severe hypoxemia and polycythemia) had no hypoxic response, nine had normal responses, and one had an above-normal response.

Bradley et al. (41) measured ventilatory and $P_{0.1}$ responses to progressive hypoxia in 20 COPD patients with chronic hypoxemia and 17 COPD patients with normoxemia but similar pulmonary function defects. In 12 of 20 hypoxemic patients, and 3 of the 17 normoxemic patients, no ventilatory or $P_{0.1}$ response to hypoxia could be convincingly demonstrated. Measurable responses in both $\dot{V}_E$ and $P_{0.1}$ were lower in the hypoxemic patients than the normoxemic ones. This was true even though eight of the hypoxemic patients also had some $CO_2$ retention at the time of the test.

Fleetham et al. (47) reported data on 30 patients with chronic hypoxemia who had been treated for 6 months with home oxygen. Their blunted hypoxic responses did not improve with treatment, but were actually further reduced in those patients who used oxygen 24 hr/day. At the same time, ventilatory response to $CO_2$ was reduced and there was a rise in resting $P_{CO_2}$.

Another method for testing sensitivity to hypoxemia is to administer oxygen to hypoxemic patients and observe the resulting transient decrease in ventilation (96). This method has been used in COPD (97). The results of the test are reported to correlate poorly with results of hypoxia stimulation tests (98). Interpretation depends on knowing the change in $P_{O_2}$, the starting $P_{O_2}$, the $P_{CO_2}$, and the rapidity of the rise in arterial $P_{O_2}$ caused by the switch to oxygen breathing. Because all

these factors are usually abnormal in COPD, comparison with normals or between patients is generally difficult. Lee and Bishop found a transient drop in ventilation of 16%. Prime and Westlake found a drop in ventilation of 5% in the steady state after 100% of oxygen was given, associated with a rise in $P_{CO_2}$ of 9 mmHg. There was a wide range of responses.

Overall, the data show that ventilatory response to hypoxia is pathologically low in some patients with advanced COPD and suggest that the chemoreceptor response is very poor in some cases. As with ventilatory responses to $CO_2$ the available methods of assessing output of the respiratory centers do not permit a clear evaluation in individual cases of how much of the reduction in ventilatory response can be accounted for by purely mechanical or muscle limitations. However, there are individual variations in chemosensitivity to hypoxia that could have a major impact on ventilatory behavior in respiratory failure. Heredity probably plays an important part in determining individual responses to hypoxemia (87,90,99–102).

### *Acute Respiratory Failure*

The best information about ventilatory response to hypoxemia during acute respiratory failure comes from the study of Derenne's group (19), who switched patients from air to 100% oxygen and noted an immediate drop in ventilation amounting to 1.8 L/min on average, or 18% of the patient's initial ventilation (Fig. 10). These patients all had hypercapnia at the time, which should have increased their sensitivity to hypoxemia. The response to administration of oxygen was rather variable from one patient to the next, including some who showed very little response. Sensitivity to hypoxia correlated with sensitivity to $CO_2$. The average response to oxygen was estimated to be below that in the chronic stable state as described by Lee and Bishop (97) because the drop in ventilation was the same as in the chronic state, even though the ARF patients began with much lower oxygen and the time course of the change in ventilation was about the same for both groups.

Hubmayr and associates (103,104) have proposed assessing the chemical control system by finding the "recruitment threshold $P_{CO_2}$" for ventilation. The procedure is applied to patients on mechanical ventilation. With tidal volume and duty cycle fixed, respiratory rate is increased until there is no detectable sign of inspiratory effort on the part of the patient. After 15 min of ventilation at the same setting, $CO_2$ is bled into the inspiratory line and raised in small steps, each lasting 3 min, until the first sign of patient inspiratory effort is observed. The $P_{CO_2}$ at that point is called the "recruitment threshold." It is important to note that this threshold does not correspond exactly to the $P_{CO_2}$ at which the patient could make efforts if breathing spontaneously. First, there is evidence that mechanical ventilation by itself may exert an inhibitory effect on respiration and raise the $P_{CO_2}$ at

which subjects become apneic (105). Second, the definition of apnea in this protocol is that the patients' natural respiratory rate is slightly lower than that of the ventilator, so they make no effort just in the brief period before the next ventilator cycle. Nevertheless, if ventilator settings are constant throughout the experiment, it is possible to look for changes in the threshold in response to other manipulations. When oxygen was administered to COPD patients treated for acute failure (median 13 days on the ventilator before the study), eight of 10 patients showed an increase in recruitment threshold (mean for the 10 patients, 3 mmHg). This observation suggests that in many cases oxygen shifts the $CO_2$ response curve slightly to the right. The threshold is essentially an intercept on the $CO_2$ response curve and gives no information about the slope of the curve.

Altogether, the evidence shows that many hypoxemic patients in acute respiratory failure are sensitive to hypoxemia, and hypoxic stimulation can be responsible for an important component of ventilation, but sensitivity to hypoxemia tends to be below normal and is absent in some patients. It is difficult to say how far from normal the responses are of most of these patients' chemoreceptors to hypoxia. In addition to all the problems of assessing output that make it difficult to interpret ventilatory response curves to hypoxemia, there is the additional one of interaction between $CO_2$ and hypoxia. Whereas $CO_2$ response curves can easily be performed under a standard condition of hyperoxia, it is much more difficult to test the response to hypoxia under normocapnic conditions, because most of the patients are hypercapnic. Hypercapnia augments the slope of the ventilatory response to hypoxia in COPD patients as well as normals (106), but there is no good data against which to compare the acute respiratory failure patients.

## V. Control Seen from the Point of View of the Muscles

The problem of control of ventilation can be viewed not as a problem of blood gas homeostasis, but as a problem of preserving the function of respiratory muscles in a stable state. At the point when the maintenance of $P_{CO_2}$ at its normal level can only be achieved at the cost of sacrificing function of the muscles that are the sole means of maintaining $P_{CO_2}$, it is obvious that homeostasis of these muscles becomes the primary issue for survival. The control system resembles the block diagram of Figure 12.

Respiratory muscles have their own control systems outside the control exerted over them by the system for homeostasis of blood gases. These muscle control systems seem to have three major roles: to adjust motor output to individual muscles according to changes in load or in resting length, to integrate shared use of these muscles by locomotor and respiratory control systems, and to limit activity of the muscles so as to prevent fatigue or damage. The function of muscle control systems could be altered in disease. Normally functioning systems that act

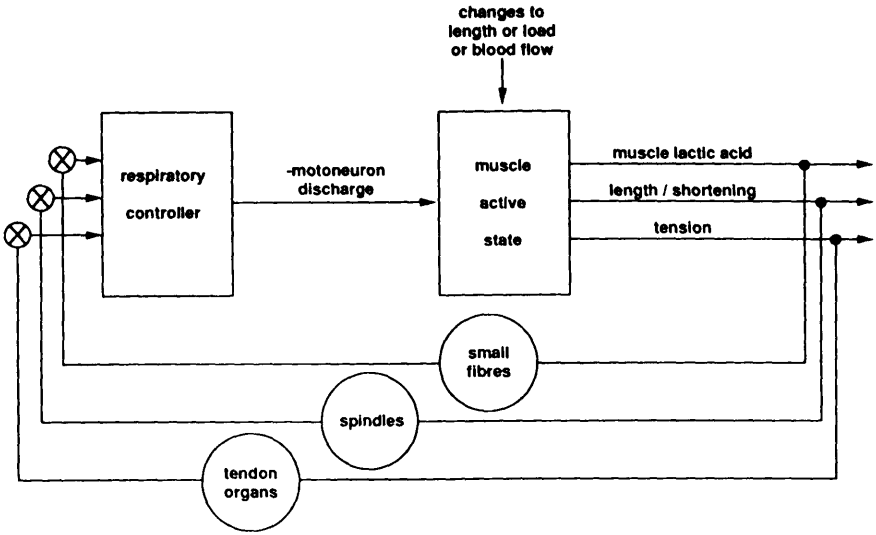



**Figure 12** Block diagram for a ventilatory control system aimed at stabilizing the conditions of contraction of respiratory muscles.

to prevent damage or fatigue may play a major role by limiting respiratory controller output under extreme conditions, such as acute respiratory failure.

### A. Mechanisms for Adjusting Muscle Activation to Changes in Length or Load

*Load-Compensating Mechanisms Available*

Most skeletal muscles have feedback from muscle spindles and tendon organs. These receptors sense length and tension in the muscle and transmit information to the spinal cord and higher centers. Detailed summaries of the available information about these mechanisms in respiratory muscles are found in recent reviews (107–109). In general, the various spinal and supraspinal reflex loops arising from such receptors have the capacity to change the gain in the transformation of respiratory center output into output of spinal motoneurons. The importance of these gain-controlling mechanisms for respiratory control in humans is difficult to evaluate. It is probably different for different muscles and for different conditions. The various muscle mechanoreceptors in many circumstances act as if their purpose was to make sure that a planned motor act, governed by a central pattern generator (a neural network that generates a stereotyped pattern of activity in the absence of peripheral input), would be completed fairly accurately, achieving the

planned motion in spite of unexpected variations in the load on the muscle. In a muscle spindle system, for example, the spindles can be driven by the gamma motor neurons to contract at a certain rate, the same as the expected rate of contraction of the muscle in which they are embedded. If the main body of the muscle encounters an unexpected load and shortens less than expected, the spindle afferents are stimulated and cause reflex excitation of the alpha motoneurons to the main muscle, which in turn contracts more vigorously and thus compensates for the unexpected load.

In the respiratory system, the planned motor act is normal inspiration and expiration. To compensate for loads, the respiratory control system can get information about whether the planned motor act is being achieved from a wide variety of sources (one of these is the chemoreceptors: a load tends to cause a decrease in ventilation and a rise in $P_{CO_2}$, which in turn stimulates the respiratory muscles to contract more strongly, but in this section we consider only the nonchemoreceptor mechanisms). Muscle spindles and tendon organs give information about individual muscle shortening and tension. (The diaphragm and parasternal muscles are less densely provided with spindles than other respiratory muscles.) Joint receptors give information about chest wall movement. Equally important, however, may be vagal lung volume receptors and upper airway flow and pressure receptors. The complexity of these interlocking systems makes it very difficult to sort out the importance of individual mechanisms, which are likely overlapping and redundant and likely influence the effectiveness of one another.

### *The Loading Response*

The "loading response" refers to the observation that, in the absence of chemoreceptor feedback, the electromyogram (EMG) and pressure output to respiratory muscles increase shortly after a load is suddenly applied to the respiratory system. It is probably the sum result of many nonchemical control systems for muscle activity (110–112,287). Much of this response is not immediate but begins several hundred milliseconds after the beginning of the first loaded breath. It develops fully after two or three loaded breaths and depends on memory of the loading conditions in preceding breaths. The sensory input required and the central integrating mechanisms are not defined. Sensory input may come from chest wall length or tension receptors, from vagal volume receptors, or from the upper airway. Integration must occur at least in part at a supraspinal level because the response includes alterations in inspiratory and expiratory timing.

The typical response to addition of an inspiratory resistive load in normal subjects is seen most easily as an increase in occlusion pressure or electromyogram (EMG). The standard experiment is to have subjects breathe through a circuit in which a resistance is added, usually on inspiration only. Breathing is then stimulated with $CO_2$. The slope of the ventilatory response curve is compared with

the slope in the unloaded condition. The output of the controller is assessed as occlusion pressure or EMG. Normal subjects with inspiratory resistive loads show a decrease in resting ventilation and in ventilatory response to $CO_2$, but also show an increase in resting occlusion pressure and in occlusion pressure response to $CO_2$ (113–115,286), indicating that respiratory motor output has been increased by the load, independently from any chemoreceptor effect. Often the load causes a change in tidal volume/frequency ratios over and above that expected just because of the increase in overall output.

When the same test is applied to COPD patients in a stable state (not in acute failure), their loading response is found to be reduced or absent (116–118). The same was true when internal resistance was increased with methacholine (119, 120). This has been interpreted to mean that these patients have a defect in the normal loading response, but that conclusion is not necessarily valid. One problem is that the scatter in occlusion pressure measurements makes it difficult to discern small changes in $P_{0.1}$. Another is that the conversion of motor output to pressure may be poor in COPD patients, so that a given increase in motor output may produce a smaller pressure increase in COPD patients than in normals. Finally, it is possible that the loading response is already engaged in the COPD patients because of their intrinsic load, and the extra load put in place during the test evokes a lesser response because of nonlinearity in the load-response curve. The reverse experiment in which the intrinsic load is reduced by giving a bronchodilator resulted in a decrease in diaphragm EMG without a change in blood gases (13), suggesting that the COPD patients do have some contribution to motor output through a loading response. One study of external resistive loading has been done in patients recovering from acute respiratory failure (121) and detected no increase in occlusion pressure with loads of 2.5 and 5 $cmH_2O/L/sec$, but these loads are smaller than the ones that are usually needed to elicit a measurable loading response in normal subjects. The response to expiratory resistive loading also seems to be attenuated in patients with stable COPD (122).

In fact, Lopata et al. (123) found in rebreathing experiments that some COPD patients with an inspiratory resistive load did increase their diaphragmatic pressure output (swing in $P_{di}$ per breath) and improve the $P_{di}$ they achieved for a given diaphragm EMG ($P_{di}/E_{di}$), but other COPD patients showed a decrease in $P_{di}$ and in $E_{di}$ with the load. The change in $P_{di}$ with the load correlated with the FRC of the patients. Those with very high FRC showed a decrease in $P_{di}$ with the load, while those with low FRCs showed an increase in $P_{di}$. Those who improved diaphragm function with the load also showed an increase in the swings in gastric pressure with respiration, and those who deteriorated showed a decrease in gastric pressure swings. The data suggest that a high end-expiratory volume interferes somehow with the ability of the respiratory pump to respond to an added inspiratory resistance. The mechanism for this remains speculative, but the effect could be important in acute respiratory failure, when end-expiratory volume is probably increased above its level in the stable state. The results emphasize again the

importance of interindividual variations in performance of the ventilatory control system.

Santiago et al. (117) noted that administration of narcotics depressed the response to resistive loading in normal subjects. They postulated that endorphins might be secreted in abnormal amounts in patients with severe COPD in order to reduce their level of chronic discomfort and might be responsible for the poor response to added resistive loads. To support this hypothesis, they administered naloxone to COPD patients and found that the loading response was restored in the seven patients who had no measurable response and was enhanced in the other seven. However, when Simon et al., (124) repeated this experiment with a double-blind control design, they were unable to find any effect of naloxone. Naloxone also had no effect on blood gases of COPD patients in ARF (125). In awake goats, Scardella et al. (126) found that several hours of flow resistive loading did produce a rise in CSF β-endorphin, and Scardella et al. (127) found that naloxone caused the animals to defend tidal volume better in response to inspiratory resistive loading over 2 hr. They noted in these animals that the higher tidal volumes with naloxone in loaded animals were not due to an increase in diaphragm EMG, but were associated with abdominal expiratory activity, assessed by increases in expiratory gastric pressure. A subsequent report showed that naloxone did indeed increase the EMG of abdominal expiratory muscles, supporting the hypothesis that endorphins were responsible for impairing the abdominal muscle response to sustained loading (126). The significance of these findings in goats for patients with COPD is unknown. COPD patients do use abdominal expiratory muscles (16,128), but it is not known whether this is due simply to a high overall output of the respiratory centers or is partly a loading response.

Petrozzino et al. (129) found in the awake goats that the spectral shift of diaphragm EMG induced by inspiratory resistive loading could be reversed by naloxone, pointing again to a role of endorphins in the neural response to heavy loads and also suggesting that the spectral shift associated with fatigue might be partly due to changes in the pattern of motoneuron recruitment with the heavy load, and not purely due to a change in muscle fiber conduction velocity.

Many reports fail to mention a major consideration for COPD in all these loading experiments, namely the effect the load has on tidal volume and frequency, as opposed to its effect on output assessed simply as ventilation, occlusion pressure, or inspiratory EMG. Oliven et al. (119) induced bronchoconstriction with methacholine in COPD patients and found that ventilation as well as $P_{0.1}$ actually increased with increasing airways resistance, but that arterial $P_{CO_2}$ increased as well. The patients who had larger increases in $CO_2$ shortened their inspiratory time in response to the load and failed to increase tidal volume. Those whose $CO_2$ rose only slightly increased their tidal volume more and decreased their inspiratory time less in response to the load. In a related experiment, the same authors added external resistive loads to both inspiration and expiration in COPD patients and found that some had a large increase in $CO_2$ and some a small increase

(130). Those with a small increase in $CO_2$ showed an increase in tidal volume and a reduction in frequency. The mechanisms responsible for the variations in tidal volume versus frequency response in these patients were not identified, but they clearly had a large influence on gas exchange.

#### *Length-Restoring and Length-Compensating Responses*

A second kind of adjustment of muscle activity is the response to a forced change of length. Each muscle has an optimal length and normally operates close to that length. When it is not at its optimal length, it will generate less tension for any given degree of activation and will be less effective and less efficient. The optimal length for most inspiratory muscles is normally close to their length at FRC. When a reduction in end-expiratory length is forced on the diaphragm (the only respiratory muscle studied in this regard) by means of positive end-expiratory pressure, two kinds of responses are elicited. *Length-restoring responses* consist of the activation of other muscles (abdominal expiratory muscles) that raise abdominal pressure at end-expiration, pushing the diaphragm dome upward and restoring its end-expiratory length to near normal. *Length-compensating responses* consist of an increase in activation of the muscle, so that it will generate the expected amount of tension in spite of its shorter length. These responses have been little studied in humans. They do exist (131–133) but are not demonstrable under anesthesia (134). Their potential role in the acute hyperinflation of acute respiratory failure or the chronic hyperinflation of severe COPD is unknown.

### B. Interaction with the Locomotor System

The muscles that we think of as being devoted to the purpose of respiration also participate in various postural and locomotor activities. The interaction between postural and respiratory control has been studied in COPD patients who are asked to do exercise with unsupported arms, compared with exercising by means of an arm ergometer that supports the weight of the arms. Needing to use rib cage muscles to support the weight of their outstretched arms, the patients became short of breath rapidly and altered their breathing pattern in a way that suggests relatively greater contribution of the diaphragm and expiratory muscles and relatively less contribution of inspiratory rib cage muscles (135). During arm exercise, compared to leg exercise, COPD patients more quickly develop dyspnea and dysyncrhonous breathing (136).

### C. Mechanisms that Might Limit Muscle Activation in Extreme Conditions

Respiratory muscles could damage themselves or the structures to which they are attached or could become fatigued from sustained effort and no longer be able to continue generating the tensions and pressures required of them. Mechanisms that

can help the individual to avoid such extreme conditions include the behavior of avoiding exercise or of assuming a posture that gives maximum advantage to the respiratory muscles (137). There are also afferent feedback systems from muscle that tend to inhibit motor output to muscles that are approaching their limits. Golgi tendon organs are sensitive to tension generated by a muscle's own contraction, and their afferents tend to inhibit motor output to that muscle. Their specific role in respiration is unknown. Recent studies have provided evidence for a feedback system mediated, at least in part, by tonically firing small fiber afferents that can be activated by fatiguing the muscle, by intra-arterial infusion of lactic acid, or by electrical stimulation and have the effect of inhibiting motoneurons to the muscle (109,138). Experiments with electrical stimulation show that some small fiber afferents in the phrenic nerve can increase the activation of respiratory muscles (139,140), but the physiological stimulus to fibers with this effect is not known.

Respiratory muscle lactic acidosis that develops during inspiratory resistive loading in unanesthetized animals is associated with a degree of inhibition of the individual muscles that is proportional to the degree of acidosis in the muscle and seems to be mediated by endogenous opioids, since it is largely reversed by naloxone (141). This mechanism apparently explains in part the changes in distribution of respiratory muscle activity seen during inspiratory resistive loading in these animals (126,141). The same authors propose that muscle lactate through a non-opioid-dependent pathway plays a role in stimulating respiratory effort during inspiratory resistive loading (129,141).

These various experiments show that a complex feedback system from respiratory muscles can detect changes in the muscle's environment and can either increase or decrease activation both of that muscle and of other respiratory muscles. The details of what the various afferents detect, under what circumstances they are activated, and how their effects are integrated remain to be worked out. Evidence from other muscles suggests that even the activity of individual motor units may be modulated by feedback from muscle so that within the muscle there may be reorganization of the use of muscle fibers under heavy loads (142,143). It may be postulated that such feedback mechanisms could play a key role in acute respiratory failure.

## VI. Control of Oxygen Delivery and of Temperature

The purpose of the combined cardiorespiratory system is to supply sufficient oxygen to the tissues. In fact, it has been proposed that many of the variations of the dimensions of the respiratory and cardiovascular organs across many species can be explained by calculations of the maximal rate of oxygen transfer permitted by them (144). Numerous control mechanisms exist that can act to optimize

oxygen flow to each organ. Carbon dioxide production in turn depends on the supply of oxygen to tissues, their rate of oxygen consumption, and the respiratory quotient.

In acute respiratory failure of COPD, the oxygen delivery system is stressed in several different ways: the overall requirement for oxygen may be increased in the resting patient by the increased oxygen consumption of respiratory muscles or by fever due to an infection. The ability of the circulatory system to deliver this oxygen is impaired by arterial hypoxemia, and possibly by polycythemia interfering with flow in some capillary beds, especially the brain (145). Blood flow to the diaphragm may be reduced because of high resistance in the diaphragm circulation due to very strong contractions of the muscle (146,147). Overall cardiac output may be impaired by high resistance in the pulmonary circulation and by heart-lung interactions (described in Chapter 9) as well as by hypoxemia and acidosis of blood supplied to the myocardium. Vasodilatation caused by hypercapnia, acidosis, and medications might increase blood flow more than needed in some circulatory beds. It is certainly conceivable that some severely hypoxemic patients in acute respiratory failure may fail to supply oxygen to all their tissues at a rate sufficient to supply the demands of metabolism (i.e., may have "oxygen delivery–limited oxygen consumption"). Low cardiac output can result in low mixed venous oxygen content and $P_{O_2}$. This in turn contributes to low arterial $P_{O_2}$ because of low $\dot{V}/Q$ units.

From the point of view of optimizing oxygen delivery, the ventilatory control system might be adjusted in several ways: to control intrathoracic pressure swings in such a way as to interfere the least with venous return and cardiac output, to make use of respiratory muscles whose ratio of blood flow to oxygen consumption is not at a critical level, to let arterial $P_{CO_2}$ and pH change to values that place the oxygen hemoglobin curve in the best position for transporting oxygen from lungs to tissue, or to adjust alveolar $O_2$ and $CO_2$ to optimize function of the hypoxic vasoconstrictor mechanism to match local perfusion with local ventilation. The ventilatory control system can therefore be viewed in the perspective of a device for stabilizing cardiac output and flow distribution, as indicated by Figure 13.

Many interactions between cardiovascular variables and the respiratory controller are recognized (148). Baroreceptor stimulation tends to inhibit ventilation, and hypotension tends to stimulate ventilation. Muscle receptors, not only in muscles of respiration, signal changes in muscle environment indicative of insufficient perfusion and can stimulate ventilation. Congestion of pulmonary vessels stimulates "J" receptors that promote rapid shallow breathing. Changes in cerebral blood flow affect chemosensitivity (149). [One measurement of cerebral blood flow in patients in the ICU with COPD in ARF found no abnormality (150).] Hypoxemia causes changes in peripheral sympathetic tone that can affect both global cardiac output and local distribution of flow. Lung inflation reflexes can

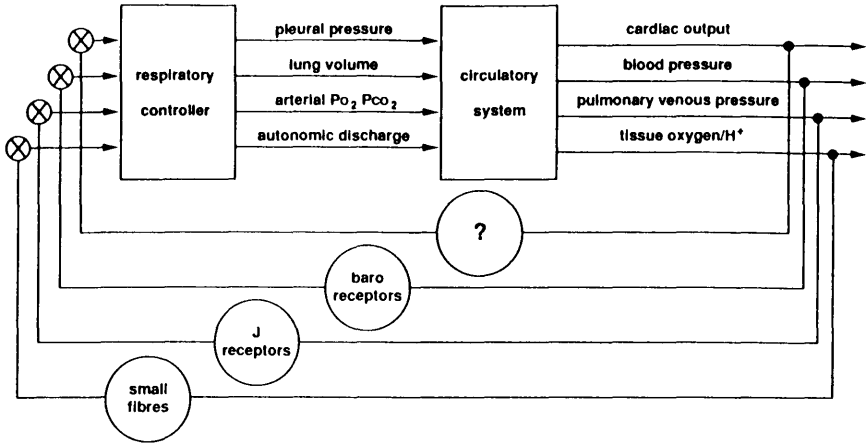



**Figure 13** Block diagram for a ventilatory control system aimed at stabilizing cardiac output and oxygen delivery.

alter systemic vascular resistance (151) and capacitance (152) and heart rate (153). Some authors have proposed that the very tight linkage between ventilation and cardiac output that is seen in exercise (29) may be due to feedback from the circulatory system stimulating ventilation.

In patients whose oxygen consumption and $CO_2$ production are partly limited by oxygen delivery, measures that improve cardiac output or arterial oxygenation could result in an increase in $CO_2$ production, and therefore in arterial $P_{CO_2}$, with worsening of respiratory acidosis. Under that circumstance, a rise in arterial $P_{CO_2}$ should be considered an indication of treatment success. Cardiac output and $CO_2$ production have seldom been measured systematically in COPD patients in acute failure, but occasional cases (104) have shown rises in $\dot{V}_{CO_2}$ with the administration of oxygen.

A related control system is the one for controlling body temperature, which tends to go up when metabolic rate goes up. The rate of heat loss increases with ventilation, and control of ventilation is linked with body temperature, not only in animals who pant. Ventilation increases with body temperature and decreases with cooling of core, skin, or upper airways (reviewed in Ref. 154).

## VII. Control of Sensation

Conscious organisms avoid discomfort and try to maximize pleasurable sensations. It is possible that, in some cases, ventilatory behavior is strongly influenced

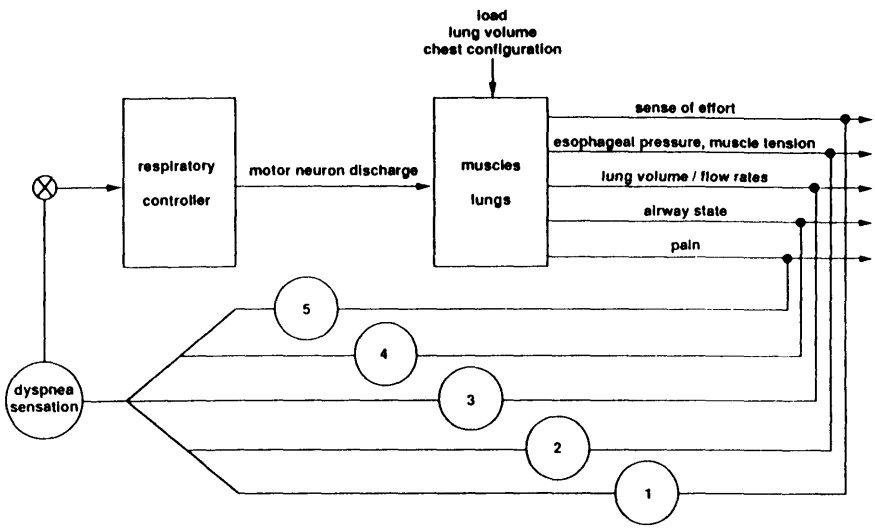



**Figure 14** Block diagram for a ventilatory control system aimed at stabilizing respiratory sensation. The feedback elements for the various quantities or qualities represented by numbered circles are either poorly defined (1) or assemblies of receptors (2–5).

by a control system whose object is to minimize dyspnea. In such a system (Fig. 14) the controlled variable is discomfort. The feedback may come directly from nocireceptors or from neural networks that generate an integrated signal corresponding to dyspnea. Current perspectives on physiology of dyspnea can be found in several recent reviews (155–162).

### A. Sources of Sensation

Dyspnea appears to arise from the integration of an array of different sensory inputs (290). Analysis of the language used by dyspneic patients to qualify their discomfort suggests as well that there are different varieties of dyspnea that tend to be associated with different diseases (118). Current views about sources of sensations mainly come from studies in which the magnitude of dyspnea is correlated with measurable physiological variables.

There is a good correlation between respiratory sensation and swings in pleural pressure in normal subjects breathing against inspiratory loads (163) with small additional contributions related to $T_I/T_{TOT}$, $f$, and muscle strength. The sensation arising from generation of pressures by one group of respiratory muscles may be different from the sensation when another set of muscles is used to generate the same pressures (164). In particular, respiratory sensation correlates

well with magnitude of electrical activity of sternomastoids and of rib cage muscles in the region of the parasternals, but not with diaphragm electrical activity in subjects who breathe against a resistor to cause diaphragm fatigue (165). The perceived magnitude of inspiratory pressure generated by voluntary contractions is greater if the diaphragm is used to generate the pressure than if the rib cage muscles are used, and less if the pressure is generated at higher lung volumes (166,167). Patients with COPD have higher threshold values for perception of added inspiratory resistances than do normal subjects (168).

Burki (169) found that 14 resting stable COPD patients with more severe disease who were breathless at rest tended to have higher values of occlusion pressure ($P_{0.1}$) than 10 patients with milder COPD who were not breathless. In a more detailed study of 15 patients all with $FEV_1$ in a fairly narrow range between 25 and 48% predicted, Robinson et al. (170) looked to see if variations in dyspnea in exercise could be correlated with "respiratory drive" assessed as $P_{0.1}$ at rest and $P_{0.1}$ response to hypercapnia and hypoxia. Those with greater slopes of response to hypercapnia and hypoxia had greater exercise ventilation and maximal $\dot{V}O_2$ but there was no relationship between $P_{0.1}$ and dyspnea. The small number of patients and scatter in the data limited the power of the study to exclude a relationship. These kinds of studies are also limited by depending on only $P_{0.1}$ to assess either "respiratory drive" or pressure generation by the respiratory muscles or the load on the respiratory muscles. In exercising COPD patients Noseda et al. (171) found dyspnea correlated best with inspiratory flow rates.

Data relating dyspnea to pressure and, to a lesser extent, other mechanics measurements can be interpreted to indicate that dyspnea sensation in subjects under these conditions arises largely from receptors sensitive to muscle tension or to pressure, with a modifying influence from volume or length receptors. Another interpretation, however, is that the sensation arises from a 'sense of effort' related to the degree of descending motor output rather than to the mechanical effect of the output. This idea is supported by experiments in which the respiratory muscles are weakened by fatigue (172) or curare (173), which find that when the weakened subject makes the bigger effort that is needed to generate the same pressure as before he was weak, the sensation increases. Similarly, subjects who increase the strength of their respiratory muscles by training, then have reduced sensation for the same inspiratory mouth pressure (174).

Abnormal blood gases may by themselves cause dyspnea, but this is questionable. Hypoxemia or hypercapnia leads to increased respiratory efforts, which could be the proximate source of the sensation. When these are controlled for by experimental design (175) or eliminated by complete paralysis (176), some authors have found some evidence to suggest direct dyspnea-causing effects of both hypercapnia and hypoxia, but Campbell et al. (177) found no dyspnea in volunteers made apneic with curare and stimulated with $CO_2$.

Receptors in the airways have been implicated as a source of respiratory

sensation in the few human experiments in which vagal afferents were blocked with lidocaine (178–180). Unfortunately, these experiments were performed before standard methods of quantifying respiratory sensation were established, and before the correlations were recognized between sensation and respiratory pressures, which were not measured in those experiments. In stable COPD patients more recently, O'Donnell et al. (122,181) have provided good evidence that airway collapse due to expiratory flow limitation occurs occasionally at rest, and much more often in exercise. Addition of external resistive loads that reduce the extent of airway collapse is associated with a decrease in dyspnea, suggesting that some of the unpleasant sensation is coming from receptors in the trachea or bronchi.

Lung hyperinflation developed during exercise has been correlated with dyspnea in stable COPD patients by O'Donnell and Webb (182). They measured dyspnea on a Borg scale during progressive exercise in 23 COPD patients with $FEV_1$ averaging $0.94 \pm 0.09$ L and found that it correlated best with the degree of dynamic hyperinflation and to a lesser extent with tidal volume and breathing frequency. In exercise those patients with the most dyspnea had higher ventilation for a given work rate, their end-expiratory volume increased more, and their end-inspiratory volume was closer to TLC. The increased dyspnea could be related to the greater pressure and effort required of the more disadvantaged inspiratory muscles. Interestingly, another study of 10 exercising COPD patients with a slightly different protocol (183) found that the increase in dyspnea was least in those who had the greatest rise in end-expiratory level. The authors found explanations for this opposite finding in data indicating that perception of tension in respiratory muscles is blunted at high lung volumes (166) and that parasternal muscles may become relatively more effective at high volumes and may be preferentially recruited as exercise progresses (184–186).

In dynamic hyperinflation, the airway receptors implicated by O'Donnell et al. (187) could also be important, because the rise in end-expiratory level is strongly associated with expiratory flow limitation. Positive airway pressure relieves dyspnea in COPD patients during exercise (181) and also during weaning from mechanical ventilation (188), but the effect is probably related to a combination of reduction in muscle effort with a change in upper airway stimulation.

Receptors in the face, nose, and throat also provide an important source of respiratory sensation. Cold receptors in the nose and pharynx are sensitive to inspiratory flow when inspired air temperature is less than 22°C and stimulation of them can inhibit respiration (189–191). Anesthesia of the nose causes an increase in dyspnea of COPD patients, although the sensation of flow in the nose from oxygen cannulas at ordinary flow rates does not seem to be important in this regard (192). Stimulation of facial receptors by streams or air also reduces dyspnea in some cases (193), and in normal subjects breathing with a mouthpiece, anesthesia of mouth receptors or breathing of warm humidified air increases breathlessness (194). Upper airway or facial sensory systems may explain why some patients in

acute respiratory failure rebel against having masks on their faces and may provide a mechanism by which upper airway infection or congestion could have a secondary effect on dyspnea and on control of breathing.

### B. Effects of Sensation

It is often assumed that dyspnea is in some way a good indicator of the state of the respiratory pump, and that strategies that reduce dyspnea, short of sedatives or opiates, would at the same time be good for the welfare of the pump itself. For example, dyspnea that correlates with respiratory muscle effort or with inspiratory intrathoracic pressure could be considered part of a feedback system whose purpose is to prevent overstressing the muscles. In general, strategies apparently forced on the patient by the need to avoid discomfort could thus be beneficial for overall survival because they correspond to strategies that are optimal for other reasons.

It is not necessarily true, however, that maximizing comfort should always lead to a response of the respiratory pump that is optimal for survival. A pleuritic pain, for example, may promote shallow breathing or reduced ventilation that is detrimental. A behavior that may be irrelevant to survival but important for comfort is pursed-lips breathing, which produces no convincing change in blood gases or pattern of ventilation, but may only serve to add a downstream resistance to expiratory flow, raise intraluminal pressure upstream, and prevent flow limitation from occurring in the intrathoracic airways, which collapse, vibrate, and cause discomfort when the lips are not pursed (187).

Assuming that dyspnea is one part of a feedback system that helps keep the system from being overloaded, the amount of discomfort felt by some patients for the same amount of mechanical input may be quite different from that felt by others. Those who are acutely aware of dyspnea will tend to restrict ventilation more for a given physiological deficit than those who are relatively insensitive. Normal subjects who have sensitive perception of inspiratory resistive loads show more ventilatory depression with loads that those who have less sensitive perception (195). Dyspnea thus can act as an inhibitory feedback system with quite different gain in some patients than others. Furthermore, the gain in this system could be affected by mood, lack of sleep, and a variety of drugs with effects on the nervous system. Asthma patients who have suffered near-fatal attacks have less acute perception of dyspnea than other asthma patients (196), which suggests, in asthma at least, that high gain in the sensation feedback system may give a survival advantage.

Oliven et al. (197) advanced the hypothesis that the intensity of sensations experienced during breathing by patients with COPD might affect their ventilatory response to loading and showed that the patients whose perception of intrathoracic pressure was more acute tended to defend tidal volume less well when exposed to

external resistive loads or an increase in internal resistance produced by methacholine. These data provided direct support for the concept that there are interindividual differences in acuity of perception of pressure or muscle tension, and that the need to maintain a certain level of comfort can have an important influence on ventilatory control in COPD.

When stable COPD patients are given opioids, they have a reduction in dyspnea and at the same time an increase in exercise tolerance (198–200). This can be interpreted to mean that their ventilatory limit is determined by the urge to avoid discomfort rather than by a real physiological limitation. At the point where they gave up exercising while on the opioids, however, they may have had higher ventilation, been closer to or beyond their "fatigue threshold," or had worse oxygenation and higher $CO_2$ than before the opioid. The data do not permit a conclusion about these details.

Closely related to control of sensation is the question of mood. Patients with COPD close to ARF may be anxious or depressed and their moods may fluctuate. Either of these mood states may have an effect on perception or on feedback to the respiratory controller via sensations or on effector mechanisms. Depressed asthmatics are unable to activate their diaphragm fully (201). The influence of anxiety is hard to assess, but there is certainly a class of patients with severe emphysema, often of the "pink puffer" type, who have marked fluctuations in dyspnea not associated with measurable changes in blood gases or mechanics. Effects of dyspnea on controller output in these patients may be important. For example, it is possible to imagine a sequence of events where anxiety and a feeling of not getting enough air may provoke the patient to increase respiratory efforts, increase $V_T$, and push the tension-time index of the diaphragm closer to a fatigue threshold, possibly even precipitating ARF.

## VIII. Control of the Lung

The function of the lung itself is affected by modifications to the output of the respiratory controller, and there are feedback systems from the lung that have an influence on the controller. Control of respiration can thus be considered from the point of view of controlling lung function, tidal volume, end-expiratory volume, pattern of flow and volume, bronchomotor tone, and respiratory frequency (Fig. 15). The afferent pathways for sensory receptors of the lungs lie in the vagus nerve. (Afferents from the upper airways will also be considered in this section.)

### A. Slowly Adapting Stretch Receptors

There is very extensive literature on the effects of feedback from slowly adapting stretch receptors (202,203), mainly based on observations in cats, rabbits, and dogs, usually anesthetized or decerebrate. Data from awake animals are fewer.

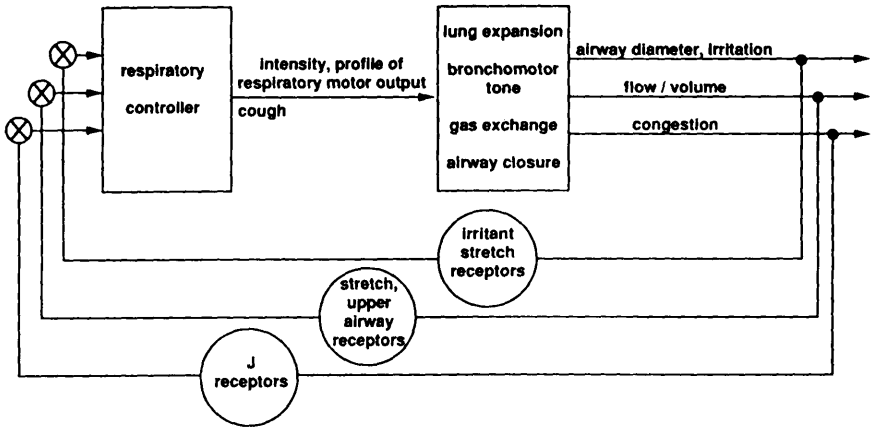



**Figure 15** Block diagram for a control system aimed at stabilizing the state of the lungs.

Because the studies that give clear information about the role of vagal receptors require cutting or blockade of the vagus nerve, there are few convincing data from humans, so concepts of the possible role of these reflexes in humans are based on observations of behaviors in humans that seem analogous to behaviors of intact animals that are known to be due to vagal reflexes. [Patients with heart lung transplants have been studied to try to find how breathing in humans is controlled in the absence of vagal feedback (204).] In normal animals, slowly adapting stretch receptors located in the trachea and bronchi convey information to the brainstem about instantaneous lung volume during inspiration and expiration and about end-expiratory volume. They are responsible for the increase in breathing frequency that accompanies stimulation of respiration by carbon dioxide. Using vagal feedback, animals maintain a constant stereotyped pattern of expiratory flow in spite of changes in expiratory resistance, by adjusting laryngeal aperture, inspiratory muscle braking activity in expiration, and expiratory muscle activity. Information about end-expiratory volume from vagal receptors provides the afferent input for reflexes that activate expiratory muscles to defend normal end-expiratory volume in the face of externally applied PEEP. Imposed high end-expiratory volume through stretch receptor feedback also tends to prolong expiratory time and shorten inspiratory time.

If they are active in humans, such reflex loops could obviously play a crucial role in COPD, and particularly in acute respiratory failure. Through the effects of stretch receptor stimulation, the rise in end-expiratory level due to intrinsic PEEP ($PEEP_i$) could be expected to cause a shortening of inspiratory time and lengthening of expiratory time, which in itself tends to reduce $PEEP_i$. It could also affect

the amount of inspiratory muscle activity in expiration, thus modifying the work and oxygen requirements of inspiratory muscles and the mean intrathoracic pressure.

Several studies of normal humans have searched for indications of stretch receptor activity. In $CO_2$-stimulated breathing Clark and von Euler (205) found a relationship between inspiratory time and tidal volume that resembled the pattern found in anesthetized cats (i.e., a progressive shortening in $T_I$ as $V_T$ increased and shown in the cats to be due to vagal feedback), but there was an apparent threshold effect in humans with no sign of vagally mediated shortening of $T_I$ until tidal volume exceeded about 1.5 L. In anesthetized cats, in the converse experiment in which $V_T$ is reduced by adding mechanical loads to inspiration, $T_I$ is progressively lengthened as $V_T$ is reduced. This effect is present in humans anesthetized with enflurane, including COPD patients (206) but is reduced by halothane. Anesthetized humans do show a brief period of apnea when their lungs are suddenly inflated, an effect ascribable to stretch receptor feedback (207). Aerosolized lidocaine, which may attenuate stretch receptor feedback, has shown some small, but variable, effects on ventilation, tidal volume, and frequency in some experiments on normal subjects (207–213).

Altogether, although there is little clear evidence of stretch receptor modulation of respiration in humans, the scanty data leave open the possibility that this mechanism could be important in normal or disease states. In anesthetized COPD patients, the stretch receptor influence on respiratory timing during normal tidal breathing is apparently less than in normal subjects (134,206). Younes has proposed that the collapse of central airways during expiratory flow limitation, which would send a misleading stretch receptor signal corresponding to small airways and low lung volumes, could be part of the mechanism favoring the apparently inappropriate pattern of breathing seen in exercising COPD patients (214).

### B. Irritant Receptors

The second major class of lung afferents are irritant receptors, which are located mainly in the larynx, trachea, and major bronchi. Stimulation of those high in the airway causes cough. Those lower down are more likely to cause bronchoconstriction and rapid shallow breathing.

Sorli et al. (215) postulated that bronchial inflammation could be responsible for the high respiratory rate and low tidal volume seen in COPD, and especially in acute respiratory failure. This hypothesis was tested clinically by Murciano et al. (216) in patients with COPD in the intensive care unit with acute respiratory failure. They lavaged the large airways through a bronchoscope with a solution of lidocaine and compared the results to a control maneuver where the airways were lavaged with an equal volume (approximately 10 ml) of saline. As shown in Figure 16, lidocaine did produce some slowing of frequency and increase in tidal volume. However, at the same time a significant drop in arterial

$P_{O_2}$ occurred. Lidocaine applied to the airways by aerosol is known to eliminate the cough reflex and therefore to abolish the function of the superficially located irritant receptors. It may also inactivate stretch receptors and partly eliminate reflexes due to them. The increase in tidal volume and decrease in frequency should by itself have improved the clinical state of these patients by improving the deadspace-to-tidal-volume ratio. The drop in oxygen indicated that lidocaine in the airways had other, detrimental effects, however, and suggested that the net, overall effect of airway reflexes in these patients was beneficial. Possible detrimental effects of lidocaine might have included a reduction in end-expiratory volume with increased airway closure, or reduction in regional bronchoconstrictor tone that might have been helping to match $\dot{V}$ to Q, or an effect of lidocaine on hypoxic vasoconstriction.

Feedback from irritant receptors may be responsible for the dyspnea that is attributable to collapse of the central airways during expiratory flow limitation (187) and may thus tend to keep patients breathing inside their maximum expiratory flow-volume loop.

It is obvious that preservation of the cough reflex is important for maintaining gas exchange in patients with airway secretions, but that a dry irritative cough can put an extra burden on the failing respiratory system.

### C. "J" Receptors

Small fiber afferents utilizing substance P can also have major effects. Originally described as being sensitive to pulmonary venous congestion or interstitial edema, they cause rapid shallow breathing in animals, and perhaps in humans (217). Slight vascular volume loading in COPD patients in acute failure causes an increase in breathing frequency and in occlusion pressure together with a deterioration in $O_2$ (218). Some of these changes can be explained by a direct mechanical effect of airway narrowing or closure by interstitial edema, but "J" receptor stimulation may also play a role. Related mechanisms play a variety of physiological roles in animals (219). The possible role of these receptors and the reflexes mediated by them in COPD remains entirely speculative.

### D. Hypoxic Vasoconstriction

The control system for matching local perfusion to local ventilation may vary in its sensitivity from one COPD patient to another, as suggested by variability in the hemodynamic response to breathing hypoxic gas mixtures (220).

### E. Effects on the Lung

In studies on normal humans and patients, it is seldom possible to attribute a change in behavior of the controller specifically to lung receptor reflexes, because

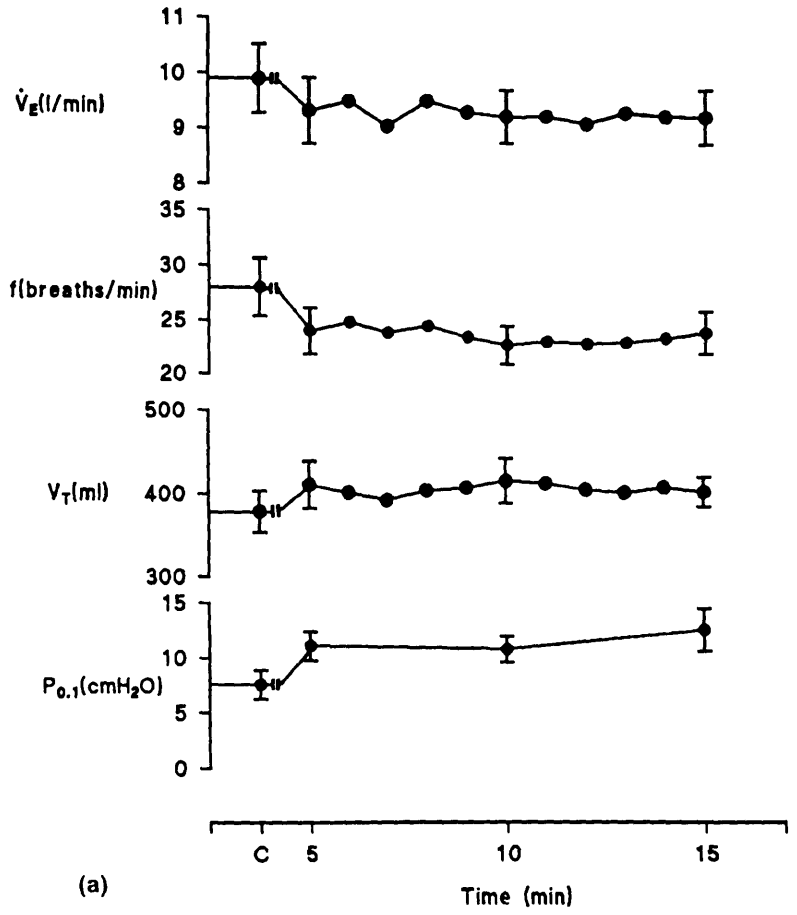



**Figure 16** Effects of instillation of lidocaine into the airways of COPD patients with acute respiratory failure. (Modified from Ref. 216.)

most observed behaviors can be explained just as well by hypotheses involving chest wall receptors, chemoreceptors, upper airway receptors, or supratentorial influences. Analogies from animal experiments would permit lung receptors to govern the choice of breathing rate, $T_I/T_E$ ratio, flow pattern in inspiration or expiration, and end-expiratory volume, most of which can have important effects on gas exchange, on respiratory resistance and compliance, and on respiratory muscle function. Probably in COPD these reflexes overlap considerably in their function with other feedback systems. It is not clear when they are important

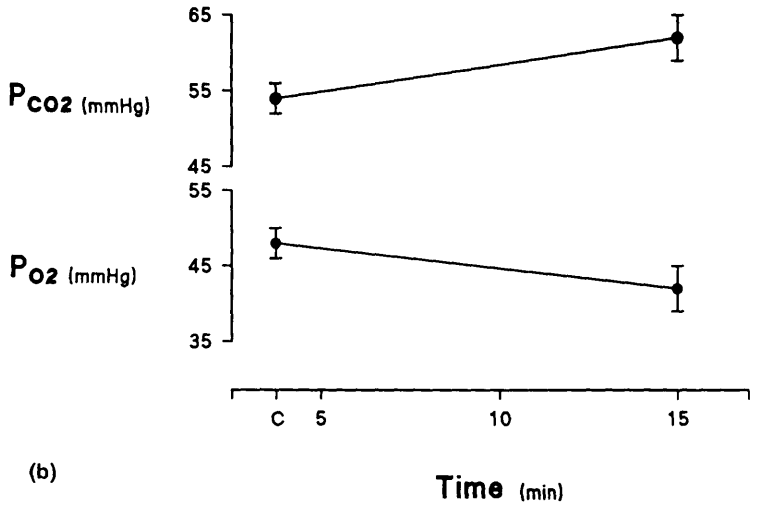



**Figure 16** (Continued)

factors. Alterations in arterial carbon dioxide and oxygen levels can also influence bronchomotor tone through reflexes mediated by chemoreceptors (221); hypercapnia decreases and hypoxemia increases bronchomotor tone.

The need to optimize lung function may conflict with other needs. The lungs of a COPD patient can be expected to function best at a relatively high lung volume where airways are more open, inspiratory resistance is lower, and maximal expiratory flows are higher, but not so close to TLC that compliance is low. Breathing at high volumes is costly to respiratory muscles, however (222) and may cause more dyspnea (182).

## IX. Interaction of Control Systems

To describe and understand interactions between interlocking control systems is obviously very difficult. Several approaches have been used.

### A. Effects of Other Systems on Response Curves to $CO_2$

The effects of other control systems can be assessed by their effects on the response curve to $CO_2$. Hypoxic ventilatory response can be expressed as a change in slope of the ventilatory response to $CO_2$ and the effect of metabolic acidosis as a change in the intercept. The loading response increases the slope of the occlusion pressure response to $CO_2$ and the intercept at resting ventilation. Vagotomy has

little effect on slope or intercept, but changes the tidal volume frequency relation. Systemic hypertension reduces the slope of the ventilatory response.

Some of the other control systems discussed in this chapter are less susceptible of precise measurement. Muscle feedback systems that act to avoid muscle overload could be expected to be alinear, with little effect at low levels of output, but a large effect at high output. Similarly, feedback based on discomfort may act mainly at high levels of output.

If the output of the respiratory lower motoneurons remains normal at rest and in response to $CO_2$ stimulation, but a mechanical load is placed on the system (e.g., an added resistance or elastance), then ventilation will be less than normal at all levels of $CO_2$ (Fig. 17) in spite of compensation by force-length and force-velocity intrinsic muscle properties. Insofar as the system is linear, the load will reduce ventilation by the same percent at all levels of $CO_2$ (line b in Fig. 17). Because of alinearities, however, there will be some tendency for the percentage reduction to be greater at higher ventilation (line c in Fig. 17). Note that the mechanical load both reduces the slope of the ventilatory response curve and increases the $P_{CO_2}$ achieved by normal resting motoneuron output. Patients with COPD do have mechanical problems that give them less ventilation for a given motoneuron output, but in spite of that they maintain $P_{CO_2}$ normal until the mechanical defect is very severe. Reversing the logic of Figure 17, it follows that COPD patients with normocapnia have higher-than-normal motoneuron output at rest. Although the slopes of their ventilatory responses are low, the slopes of their

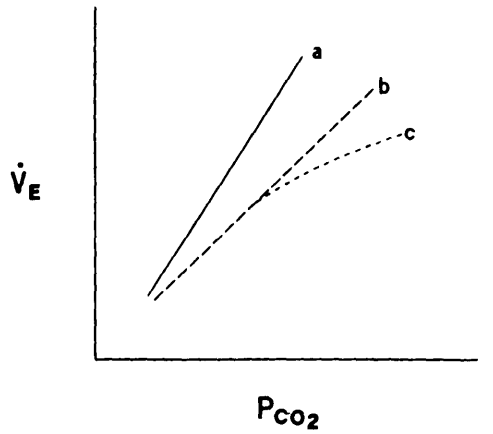



**Figure 17** Hypothetical ventilatory response curves for a normal subject (a), for a subject with normal neuromuscular output but a high mechanical load with a linear system (b), or with an alinear system (c). (For explanation see text.)

motoneuron output (equal to the ventilatory slope divided by the mechanical factor) may be normal or high. The fact that their occlusion pressure responses are normal in spite of mechanical factors that tend to reduce pressure implies that their motoneuron responses are above normal, and this is supported by the simple observation that they are using all of their respiratory muscles.

In normal subjects exposed to $CO_2$ or hypoxia to test the chemoreceptor feedback system, it is reasonable to suppose that the output measured as ventilation, pressure, or EMG is a nearly direct indicator of the degree of respiratory center activation, and the increase in output with a change in blood chemistry is a nearly direct indicator of the effect of chemoreceptor input to the respiratory center. That is, in the diagram of Figure 4, the transfer functions for neural output to muscle active state, for muscle active state to tension, for tension to pressure, and for pressure to air flow are more or less constant, and either the various feedback loops have little effect on output, or else the gain in all the feedback loops is more or less constant, so the net amplification of output caused by operation of the feedback loops is constant.

In acute respiratory failure, however, this general assumption is invalid on many counts. Many components of the system are approaching their limits, as described in Chapter 5. As a result, some transfer functions will be in a range where they are no longer close to linear. In addition, some of the feedback loops of Figure 4 may assume a greater importance than in normal conditions and may distort the output curve.

In particular, as described in Chapter 6, the transfer of lower motoneuron output to muscle active state may be altered by fatigue. The transfer of muscle active state to tension is affected by chronic changes of muscle length, by hypertrophy or atrophy, and by acute changes in length, metabolism, acid-base state, oxygenation, and so forth. The transfer of tension to pressure is altered by abnormal chest configuration at end-expiration. The transfer of pressure to flow is limited by airways resistance, respiratory system elastance, and intrinsic PEEP. All of these factors tend to make the ventilatory or pressure output of the system less than normal and less than the output when the same patient is in a chronic stable state, even if the motoneuron output is the same as it would be in a normal or a chronic stable COPD patient.

It is also necessary to consider the possibility that some of the neural feedback loops may be playing an important role in limiting output of spinal respiratory motoneurons. Such loops might be operating in a normal physiological way, but have a much greater importance than normal because of the extreme conditions in which they operate. In particular, those feedback systems that are postulated to exist for the purpose of preventing muscle fatigue by limiting muscle activity to levels that will not eventually exhaust the muscle fibers could be expected to be very active in acute respiratory failure. Other normal feedback

loops may be alinear and this may affect the overall output in ARF. For example (see Section VA), the "loading response" may be effective at small loads, but might not be able to augment output further with larger loads; i.e., the gain in that compensatory loop may decrease with higher loads.

Some feedback loops may be pathologically affected by the disorder that precipitates ARF. Bronchoconstriction or airway inflammation or pulmonary edema may excite a change to rapid shallow breathing through a vagal reflex and thus have an effect on motoneuron output. Anxiety, or depression, or sleep deprivation could also change the response of the controller to input from various receptors.

Since there are strict limits of activity beyond which muscle fibers cannot go without becoming fatigued, a feedback system designed to prevent fatigue would have to force an absolute ceiling on motor output to respiratory muscles. It follows that the motoneuron output controller curves for a system with excellent muscle-protective feedback must reach a plateau at some level (Fig. 9). If patients in ARF are close to their maximum sustainable ventilation, it is possible that they are operating in a nonlinear region of their controller curves close to a plateau. In that case the measured slope of their controller curve would be less than normal even if the overall curve is not abnormal.

Thus even the EMG response curve in COPD in ARF cannot be interpreted as a simple reflection of chemoreceptor function. It may incorporate a strong influence of other feedback loops not normally important in determining output. Shifts in the ventilatory response curve to $CO_2$ or $O_2$ may be measuring the altered influence of control systems for other variables.

Systems that tend to stabilize $CO_2$ may come into conflict with systems that tend to stabilize other variables. A crucial example is the conflict between the chemical feedback system and the system that stabilizes muscle effort or muscle oxygen consumption. A control system that is very sensitive to $CO_2$ and controls it tightly, with a steep controller curve, is necessarily a system that controls ventilation, work of breathing, and muscle oxygen consumption very poorly, because a small increase in $P_{CO_2}$ causes a large increase in work of breathing (Fig. 18). On the other hand, the implication of a flat ventilatory response curve to $CO_2$ is that ventilation and work of breathing are held close to constant in spite of wide variations in $P_{CO_2}$. The compromises that are to be made between these two requirements of a ventilatory control system in COPD and ARF have been the focus of many recent discussions (223). COPD patients who are trained to change their pattern of breathing from rapid and shallow to slow and deep (which should be advantageous for gas exchange) develop shortness of breath and are found to have gone beyond the fatigue threshold of the diaphragm as a result of developing higher transdiaphragmatic pressures with each breath (224). In many respects, the system seems to behave as though muscle-protective feedback systems become a predominating influence on ventilatory control under conditions of severe COPD.

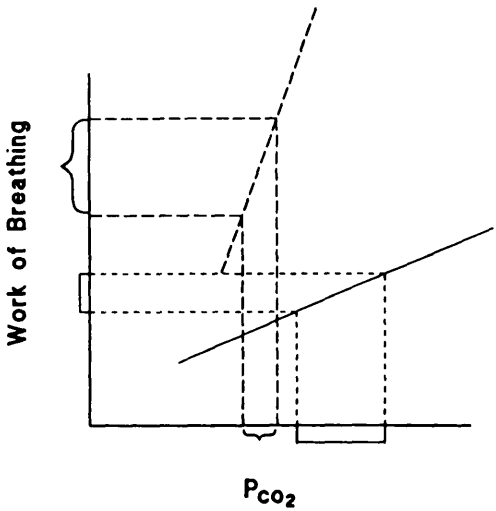



**Figure 18** Diagram to illustrate that a subject with a low ventilatory response to $CO_2$ (solid line) tends to control work of breathing closely while permitting wide variations in $P_{CO_2}$ (square brackets) while a subject with steep ventilatory response tends to control $P_{CO_2}$ tightly but permit wide variations in work of breathing (curved brackets).

### B. Modeling the Integrated System

One way to try to understand complex systems is though mathematical simulation (285). This has been done for COPD by Younes (214,225). The model focuses on the effects of different patterns of breathing when a respiratory system has the mechanical characteristics of a typical patient with moderately severe COPD, including a realistic passive pressure-volume curve for the respiratory system, increased inspiratory resistance, expiratory flow limitation, and inspiratory muscles with realistic pressure-generating capacity. Study of the behavior of this model led to several conclusions: (1) At a given inspiratory activity and frequency, the lower-than-normal ventilation in the COPD patient is mainly due to dynamic hyperinflation (rise in end-expiratory volume). (2) The degree of dynamic hyperinflation increases not only with frequency, but also with increasing amplitude of inspiratory activity. (3) At the same level of inspiratory activity, an increase in breathing frequency has limited ability to increase ventilation, because the increase in dynamic hyperinflation cannot be made without a reduction in tidal volume. (4) Expiratory muscles have a limited ability to increase ventilation, because of expiratory flow limitation. (5) A useful strategy would be to shorten inspiratory time and lengthen expiratory time (reduce $T_I/T_{TOT}$), which allows a reduction in dynamic hyperinflation.

Younes (214) points out that COPD subjects in exercise do not choose to

breathe with low $T_I/T_{TOT}$ ratios, although this seems to be the most sensible adjustment to make, but instead tend to breath at high frequency and show a considerable degree of dynamic hyperinflation. This, he proposes, may be due to expiratory flow limitation that could attenuate normal reflexes from the airway stretch receptors, which should slow the natural tendency toward tachypnea associated with large inspiratory loads and weakness of respiratory muscles.

Another modeling approach (226) incorporates a center of breathing sensation, an automatic $CO_2$ controller, a mechanical effector, and a respiratory plant, or $CO_2$ exchanger. The sensation center produces a discomfort that depends on automatic respiratory motor command and on $P_{CO_2}$ and an inhibitory input from neuromechanical receptors related to ventilation. This model can be made to simulate the results of such experiments as exercise and $CO_2$ rebreathing with and without loading with reasonable results for ventilation, $CO_2$, and discomfort, and was used to test the hypothesis (227) that ventilatory output results from an optimal compromise between the need to control blood gas levels and the need to limit respiratory mechanical effort, as well as the concept that minimization of breathing sensations could be a general principle for respiratory controls.

Although many assumptions must be made in developing these models, they offer interesting approaches to integrating multiple aspects of ventilatory control.

## X. Stability and Instability

Homeostasis is the maintenance of physiological variables close to their "equilibrium" values. "Stability" of a homeostatic system, as we use it in this section, refers to the effectiveness with which the system defends itself against an influence that tends to disturb it from its equilibrium state.

### A. Stable States

For an equilibrium steady state, we will say it is stable if it is capable of maintaining itself more or less indefinitely, with the patient alive and not subject to ongoing organ damage. By the stability of a system in such a stable steady state we mean the amount a given physiological variable will be altered by an external disturbance of a given magnitude. Stability in this sense is determined partly by intrinsic passive characteristics of the system and partly by the operating characteristics of active homeostatic control systems. It is obviously advantageous for the system to be very stable so that external events are only able to change the key physiological variables by very small amounts. When the system is intrinsically stable, there is less need for active homeostatic mechanisms to keep controlled variables near their equilibrium values.

#### *Variations in Intrinsic Stability in One-Variable Systems*

Intrinsic stability of the respiratory control system to some kinds of disturbances can be calculated from mathematical relations between controlled variables and

the factors that may be disturbed by disease. In COPD in acute respiratory failure, intrinsic stability of the system is increased in some respects and decreased in others.

### Stability of Steady-State Arterial $P_{CO_2}$ to a Change in Ventilation

The amount that $P_{CO_2}$ will change as a result of a given change in ventilation, all other things being equal, is given by the partial derivative of $P_{CO_2}$ with respect to $\dot{V}_E$ in the equation: $P_{CO_2} = K\,\dot{V}_{CO_2}/\dot{V}_E(1 - V_D/V_T)$ where $K = P_B - 47$

$$\partial P_{CO_2}/\partial \dot{V}_E = -K\dot{V}_{CO_2}/\dot{V}^2_E\,(1 - V_D/V_T)$$

The stability of the $P_{CO_2}$ to a disturbance in ventilation is the inverse of $\partial P_{CO_2}/\partial \dot{V}_E$. Stability decreases as $V_D/V_T$ increases, as $\dot{V}_E$ decreases, and as $\dot{V}_{CO_2}$ increases. For a normal subject with ventilation 6.6 L/min, $\dot{V}_{CO_2}$ 0.2 L/min, $V_D/V_T$ 0.40, $\partial \dot{V}_E/\partial P_{CO_2}$ is 6.0 mmHg/L/min. For a typical subject with COPD in ARF, with ventilation 10 L/min, $P_{CO_2}$ 60, $V_D/V_T$ 0.74, $\dot{V}_{CO_2}$ 0.2 L/min, it is 6.1 mmHg/L/min, hardly different. The system is thus no less stable in this respect.

### Intrinsic Stability of $P_{aCO_2}$ to a Change in $V_D/V_T$ Alone

From another point of view, a given increase in deadspace to tidal volume ratio ($V_D/V_T$) has a greater and greater effect on $P_{CO_2}$ when the starting value of $\dot{V}_D/V_T$ is higher, all other things being equal (228). (See Fig. 19.)

$$\partial Pa_{CO_2}/\partial V_D/V_T = K\dot{V}_{CO_2}/\dot{V}_E(1 - V_D/V_T).^2$$

In a normal subject, $P_{CO_2}$ changes 0.7 mmHg for a change of 0.01 in $V_D/V_T$. In typical COPD examples, a patient with a $V_D/V_T$ of 0.68, a $P_{CO_2}$ of 50 mmHg, a ventilation of 11 L/min, and a tidal volume of 0.4 L, who increases $V_D/V_T$ by 0.01 (i.e., increases $V_D$ by 4 ml or decreases $V_T$ by 6 ml), has an increase in $P_{CO_2}$ of 1.6 mmHg. If the starting $P_{CO_2}$ is 70, $V_D/V_T$ is 0.77, and the values of $\dot{V}_{CO_2}$, $V_T$, and $\dot{V}_E$ the same, an increase in $V_D/V_T$ by 0.01 will change $P_{CO_2}$ by 3 mmHg.

These examples illustrate that the $P_{CO_2}$ of COPD patients in acute failure is rather sensitive to changes in $V_D/V_T$ that would be too small to have an impact in normal subjects and too small to measure easily. Normal subjects, of course, compensate for any increase in $V_D/V_T$ simply by increasing minute ventilation. Insofar as their ability to increase ventilation is limited, COPD patients will show greater increases than expected for otherwise normal subjects with the same deadspace problem.

### Intrinsic Stability of $P_{CO_2}$ to a Change in $\dot{V}_{CO_2}$

Parallel calculations show that $\partial P_{CO_2}/\partial \dot{V}_{CO_2}$ is $-K/\dot{V}_E(1 - V_D/V_T)$. $P_{CO_2}$ is less stable when ventilation is low or $V_D/V_T$ is high. For a typical normal subject $\partial P_{CO_2}/\partial \dot{V}_{CO_2} = 219$. For a patient with a $P_{CO_2} = 70$ $V_D/V_T = 0.77$ and $\dot{V}_E = 11$, $\partial P_{CO_2}/\partial \dot{V}_{CO_2} = 217$, not different from normal.

### Stability of $[H^+]$ to a Change in $P_{CO_2}$

Because of high bicarbonate levels, COPD patients in ARF have $[H^+]$ values that are more stable in the face of rapid shifts in $P_{CO_2}$ than normal subjects.

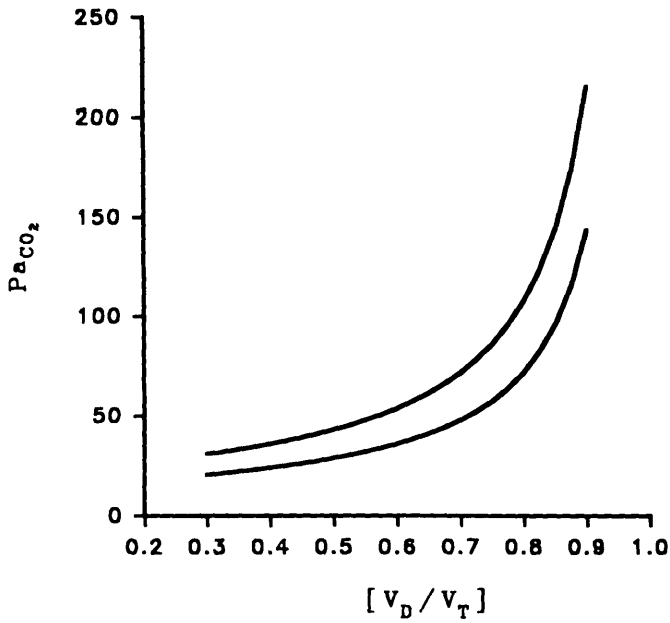



**Figure 19** Variations in $P_{CO_2}$ with variations in $V_D/V_T$ ratio when ventilation and $CO_2$ production remain constant. Lower curve corresponds to a $CO_2$ production of 200 ml/min, upper curve to a $CO_2$ production of 300 ml/min.

### Intrinsic Stability of Tidal Volume in the Face of Added Mechanical Loads

Theoretical analysis together with experimentation by adding resistances and elastances to both human subjects and experimental animals shows that most of the stability of the respiratory system to added mechanical loads is intrinsic (111). In the absence of neural control mechanisms, the percentage drop in tidal volume when a load is added to the respiratory system is less than expected if the system were completely passive. This is because of the force length and force velocity properties of muscles, which cause them to generate more force when their shortening is impeded. Allowing for this feature, the respiratory system behaves like a passive one: the decrease in tidal volume with a given added load $\Delta L$ is given by

$$V_T \text{ (\% control)} = L/L+\Delta L$$

where L is the intrinsic load on the system (229,287). In COPD, the intrinsic load is much greater than normal. A given added resistance will therefore cause a smaller percentage decrease in ventilation than in a normal person (Fig. 20). In this respect the system is more stable than normal.

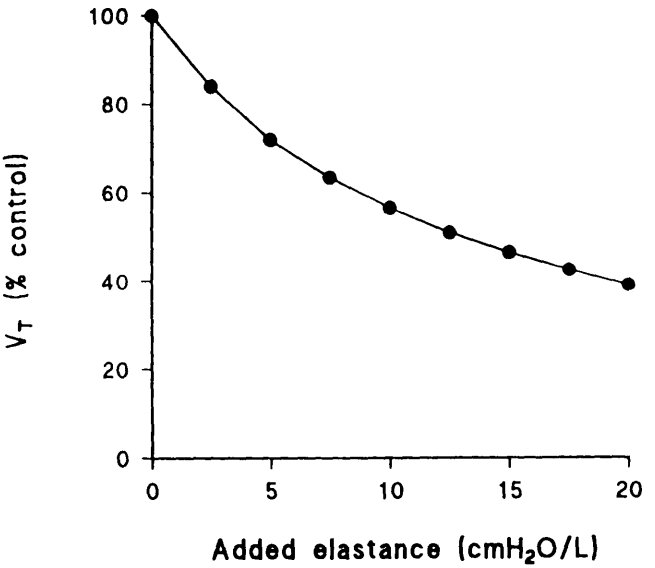



**Figure 20** Calculated effect on tidal volume of a progressive increase in mechanical load (in this case an inspiratory elastic load) in a subject with constant respiratory motor output and constant respiratory frequency. (Modified from Ref. 292.)

### Intrinsic Stability of Airways Resistance

According to the Poiseulle relationship for laminar flow, resistance is inversely proportional to airway radius to the 4th power; other flow regimes also result in disproportionately large increases in resistance as airway diameter gets small. In COPD any change in airway internal diameter has a much bigger effect on resistance to airflow than in normal subjects (230). As a result, degrees of bronchospasm, mucosal inflammation, or edema that would only trivially affect function of a normal lung can make a major difference to lung mechanics and gas exchange. Similarly, small changes in the operating volume of the lung may have an important effect on resistance and gas exchange.

### Instability due to High Oxygen Consumption and Low Efficiency of Respiratory Muscles

Any increase in respiratory work requires more oxygen and generates more $CO_2$ that has to be cleared. This limits the ability of the pump to lower arterial $P_{CO_2}$. Indeed, there is a theoretical limit when any additional effort to reduce $P_{CO_2}$ by increasing respiratory effort would be self-defeating because the increase in

alveolar clearance of $CO_2$ achieved by higher ventilation would be matched by the increase in $CO_2$ production of respiratory muscles responsible for the increase in ventilation.

### *Variations in Effectiveness of Active Homeostatic Mechanisms*

#### Responses to Hypercapnia and Hypoxia

Whatever the mechanism and interpretation of the ventilatory responses to $P_{CO_2}$ (in terms of chemoreceptor sensitivity, mechanical limitations, or interaction with nonchemoreceptor components of the control system), the measured slope, $\Delta\dot{V}_E/P_{CO_2}$, does describe the net effect of chemoreceptor stimulation. In stable COPD, and even more so in ARF, the slope is smaller than normal. The active homeostatic control mechanism that depends on negative feedback from chemoreceptors is less effective and is less able to improve on the intrinsic stability of the system to changes in $\dot{V}_{CO_2}$ and $V_D/V_T$ and $V_T$ that tend to change $P_{aCO_2}$. Increases in $\dot{V}_{CO_2}$ and $V_D/V_T$ will therefore cause a greater increase in $P_{aCO_2}$ than in a normal subject (other things being equal, namely starting values of $P_{aCO_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$, and $V_D/V_T$).

Similarly, the abnormally small value of $\Delta\dot{V}_E/\Delta P_{O_2}$ in some patients means that the net active response to a drop in $P_{aO_2}$ is less than normal and the $P_{aO_2}$ is therefore less stable in the face of disturbances that tend to decrease it, such as a worsening of $Q_S/Q_t$.

Although we have no way of testing the presumed "feed-forward" mechanisms for making ventilation match $P_{CO_2}$ in normal subjects, to the extent that mechanical and muscle factors limit the ventilatory response to chemoreceptor stimulation they must also limit the ventilatory response to feed-forward mechanisms. Again, this will reduce the stability of the system in the face of imposed changes in $\dot{V}_{CO_2}$.

#### Response to Added Mechanical Loads

As described in Section VA, there is evidence that the active response to added mechanical loads is absent or rather ineffective in COPD. As a result, the stability of the system in response to loads, though high because of high intrinsic stability, seems to gain little from active mechanisms.

#### Muscle-Protective Reflexes

Muscle-protective mechanisms (Section VC) are undetected at low levels of respiratory muscular output and are speculated to become important at high loads and high muscular outputs. Presumably the gain in this feedback system increases as a "fatigue threshold" is approached and the stability that these mechanisms confer on muscle fiber output thus increases with increasing load on the respiratory system and tends to make stability of muscle fiber condition a more and more important factor in overall ventilatory control. A real role of such a system in COPD in ARF has yet to be established, however.

### B. Unstable States

*Instability Through Positive Feedback*

By instability, we mean a condition in which the system evolves away from an equilibrium state toward one that is no longer stable and may lead to death or permanent damage to the patient.

Positive Feedback in a System with One Variable

Instability arises when there is positive feedback, so when the variable strays from its equilibrium value, the response of the organism tends to drive it even further from equilibrium. In respiratory control, the best-known example is hypoxic depression of ventilation. Normally a fall in arterial $P_{O_2}$ stimulates an increase in ventilation, which tends to raise $P_{aO_2}$ back toward its equilibrium value (Point A in Fig. 21). At very low values of $P_{O_2}$ in some preparations, however, a further drop in $P_{O_2}$ causes a drop in ventilation and therefore an even greater drop in $P_{O_2}$. The even lower $P_{O_2}$ would cause a further drop in ventilation, and so on, eventually leading to extremely low $P_{O_2}$ and the death of the organism.

Another possible example comes from the experiments of Petrozzino et al., (141), who demonstrated a feedback system in which lactic acid in a muscle stimulated an increase in muscle activity. In isolation, such a feedback loop would cause more lactic acid production, even more muscle stimulation, and eventual exhaustion of the muscle.

In a more complicated way, chronic hypoventilation tends to dull the ventilatory response to $CO_2$ and thus promote more severe hypoventilation. Similarly, prolonged hypoxemia dulls the ventilatory response to low oxygen and takes the brakes off any disturbance tending to cause more severe hypoxemia.

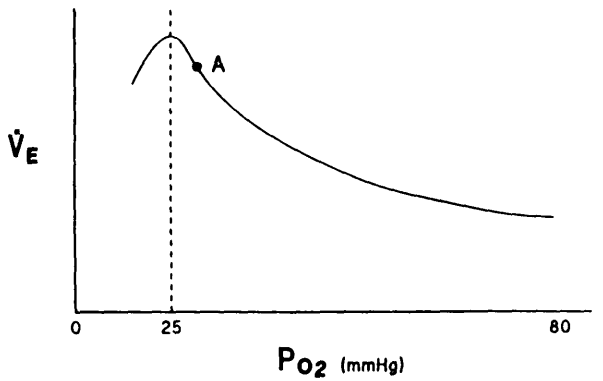



**Figure 21** Ventilatory response to hypoxia showing hypoxic depression. (For discussion see text.)

### Instability and Stability in Systems of Interacting Variables

When there is more than one controlled variable and the variables interact, many possibilities arise. New theories of complex systems that could provide a theoretical bases for analyzing such interactions have not been applied to respiratory control. Some qualitative examples can be given, however.

Some interactions between control systems can act to stabilize the whole system. For example, an organism that exhibits hypoxic depression of ventilation could be stabilized by a strong $CO_2$ feedback system that limits the drop in ventilation due to hypoxia. In a complex system, however, there may also be numerous possibilities for destabilizing positive feedback loops between interacting variables. It is easy to imagine scenarios in COPD in acute respiratory failure where such malignant interactions can take place.

Take, for example, a patient in ARF with purulent bronchitis. If a large plug of mucus should cause sudden obstruction of a lobar bronchus, there would be an immediate drop in arterial oxygen due to increased $Q_S/Q_T$. Hypoxic vasoconstriction would increase pulmonary artery pressure. This in turn would cause some reduction in cardiac output and systemic blood pressure. Together with higher airway resistance, reduced oxygen delivery to respiratory muscles could force a reduction in alveolar ventilation through muscle-protective reflexes, causing a fall in alveolar $P_{O_2}$. This, together with a fall in venous $P_{O_2}$ due to the lower cardiac output, would result in a further fall in arterial $P_{O_2}$, and so on. If the system were in a precarious enough condition, even the hypoxemia occasioned by the transient hypoventilation associated with a coughing spell or an episode of REM sleep might set off such a sequence of events.

Another example is a patient in ARF who suffers a small pulmonary embolus. This has the effect of increasing deadspace but also tends to cause rapid shallow breathing. When $V_D/V_T$ rises, the ventilatory control system is able to raise minute ventilation only slightly because of mechanical/muscle limitation. $P_{CO_2}$ rises because it is very sensitive to the increase in $V_D/V_T$. An increase in right-side filling pressures, plus the effect on myocardial contractility of acute respiratory acidosis and hypoxemia, causes a small drop in cardiac output. This, in turn, through a decrease in mixed venous oxygen aggravates arterial hypoxemia, and so on.

Another example might be a patient with COPD in ARF who also has ischemic heart disease. An episode of myocardial isochemia induced by transient hypoxemia would result in decreased contractility of the left ventricle and a rise in left atrial pressure. This would stimulate "J" receptors and cause rapid, shallow breathing as well as worsen the distribution of ventilation and perfusion and increase the (A-a) gradient for oxygen. The change in breathing pattern would cause a rise in $P_{CO_2}$ and drop in pH and a rise in end-expiratory volume and in mean intrathoracic pressure. Together these factors would further impair left ventricular function and promote a further rise in left atrial pressure and a further fall in arterial $P_{O_2}$.

### C. Transitions from Stable to Unstable States

In the one variable hypoxia-ventilation control system of Figure 21, there are two regions. As long as $P_{O_2}$ is above 25 mmHg, the system is stable because of negative feedback. When $P_{O_2}$ is below 25, the system is unstable, because of positive feedback. In fact, once the $P_{O_2}$ falls below 25, in this simple system, death of the organism will follow unless some external agent intervenes to force the $P_{O_2}$ back into the stable region. Survival of the organism thus depends on its ability to keep the $P_{O_2}$ above 25 at all times. In life, no physiological variable is completely constant. The arterial $P_{O_2}$ undergoes fluctuations due to fluctuations in alveolar ventilation, in $\dot{V}_{O_2}$, and in $\dot{V}/Q$ distribution that occur with normal activity and disease. If the resting value of $P_{O_2}$ is far from the boundary between the stable and unstable state, and if the fluctuations in $P_{O_2}$ are small, there is no likelihood of the system straying into the unstable region. On the other hand, if the resting state is close to the boundary of the stable region and if the fluctuations in $P_{O_2}$ around its resting value are not small, there is a high likelihood that the system will sooner or later fall into the unstable region. The magnitude of fluctuations in $P_{O_2}$ in response to any given change in $\dot{V}_{O_2}$ or $\dot{V}_A/Q$ disturbance depends on the intrinsic stability of the system (Section XA) and on the effectiveness of the active feedback control system for stabilizing $P_{O_2}$ in the face of perturbations of gas exchange. If the system has low stability or lies close to the boundary, a relatively small external disturbance can force it over the boundary, into the unstable region.

Exactly the same considerations can be applied to a system with many physiological variables. In that case the state of the system is characterized by the values of all the variables. If there are $N$ variables, the state of the system is described by a point in a space of $N$ dimensions. Within that space, there are regions where the system is stable. In these regions all the points (each defined by a combination of all the physiological variables) represent stable states. Outside these regions the system is unstable. Just as in the one-dimensional example, the survival of the system requires that it be in an equilibrium state that is some distance from the boundary of the stable region, so that likely perturbations in physiological variable will not bring the system over the boundary into a region where malignant positive feedback processes will force the system to destroy itself.

A system that survives, therefore, will be one that tends toward an equilibrium state that is some distance from the boundary of the region of stability and quite resistant to being changed. The distance from the boundary constitutes a sort of safety margin. The values of key physiological variables in the equilibrium state in a patient in ARF will be such that predictable fluctuations in bronchomotor tone, respiratory rhythms, $\dot{V}_A/Q$ distribution, and so on are not likely to carry the system over the boundary of the stable region and set off a malignant chain of positive feedback loops. The magnitude of the safety margin could be yet another aspect of respiratory control that varies between individual patients.

### D. Dynamic Instability

Stability as defined and discussed above refers to the stability of steady states, of equilibrium conditions where ventilation, blood gases, and other variables are averaged over minutes or longer.

Dynamic stability and instability refer to breath-by-breath variations in respiratory variables. There is normally some breath-to-breath variation in tidal volume, and respiratory frequency as respiration is coordinated with other motor functions such as swallowing, talking, exercise, or expression of emotions, and there seems to be some "random" variation as well. Tidal volume breath-by-breath in resting normal subjects has a large coefficient of variation (231). When ventilation is stimulated by $CO_2$ or exercise, it tends to become more regular, with more constant breath-to-breath tidal volume and frequency, and COPD patients even at rest have less variability in tidal volume and frequency than normal subjects (232). Near the limit of their ventilatory capacity, exercising normals or COPD patients are barely able to interrupt their regular breathing pattern long enough to speak single words.

One kind of instability in breath-by-breath ventilation is periodic breathing, which has been extensively studied and modelled (233–239). The mathematical models are based on chemoreceptor feedback in systems with $CO_2$ and $O_2$ stores and circulation delays, and they predict behavior of the human system quite well in various circumstances. A tendency to periodic breathing is seen in normal awake resting subjects and can also be attributed to feedback from chemoreceptors (68). In an experiment on normal subjects in which arterial $P_{CO_2}$ was kept nearly constant by rapidly adjusting inspired $CO_2$ concentrations according to end-tidal $CO_2$ measurements, they found that about half of the spontaneous tendency to periodic variations in breathing disappeared, and they showed in a mathematical model that spontaneous variations in blood $CO_2$ content, with realistic chemoreceptor gain and an "afterdischarge" effect whereby the effects of the $CO_2$ stimulus decayed over 80 sec, would produce about half of the spontaneous periodic type of instability they observed in normals. They postulated that other feedback loops contribute to intensify the tendency to this type of breathing instability.

In COPD patients, the tendency to unstable breathing patterns and the period of oscillations can be expected to change because of differences in $CO_2$ and $O_2$ stores, chemoreceptor sensitivity, and delays in the system. Gas exchange is also a factor. When there is a rapid drop in ventilation, as may occur during a coughing spell or an obstructive apnea, the rate of change in $CO_2$ depends primarily on $CO_2$ stores in the blood and the Haldane effect. The COPD patient with $CO_2$ retention has larger stores of $CO_2$ and is expected to have a slower rise in $CO_2$ during an episode of hypoventilation than a normal subject. The rate of fall of arterial oxygen tension during transient hypoventilation or apnea depends on

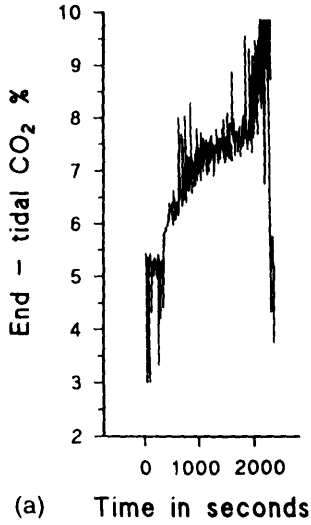
oxygen stores, but also on evenness of gas exchange, as shown in breath-holding experiments (240). Hypoxemic COPD patients in ARF have lower oxygen stores and larger $Q_S/Q_T$ than normals and can therefore be expected to show more rapid drops than normal in arterial oxygenation during brief episodes of hypoventilation.

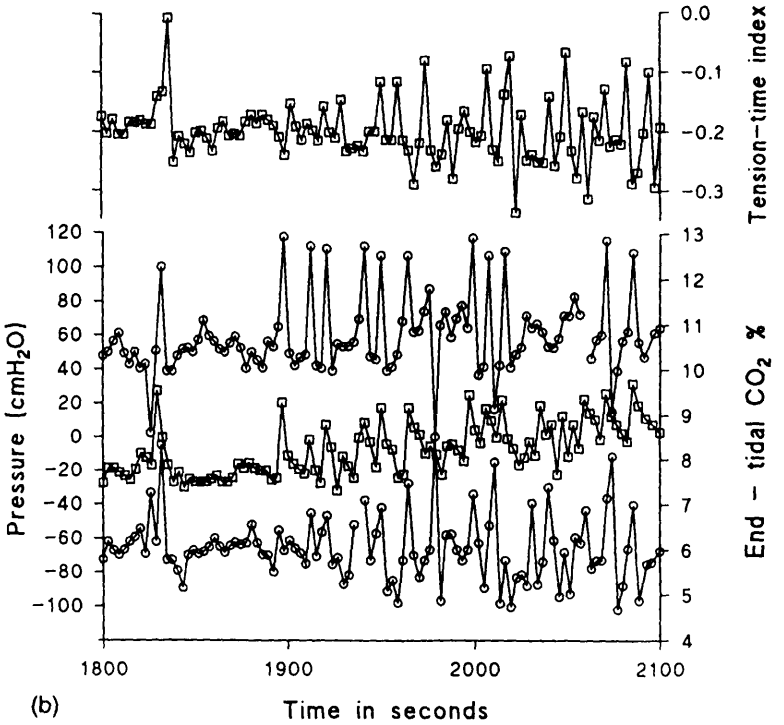
Another kind of instability in breath-to-breath ventilation more nearly resembles noise or random or chaotic fluctuations. New studies of variability of breathing based on the mathematics of nonlinear dynamics promise to bring new insights into such complex systems as ventilatory control (241–246). Modeling of simple nonlinear models shows that under some conditions the steady, regular pattern of breathing can give way to an extremely erratic pattern.

### E. Failure of the Control System

Almost all observations and discussions about control of respiration in acute respiratory failure in COPD concern themselves with quasi-steady-state conditions when meaningful measurements can be made of $\dot{V}O_2$, ventilation, cardiac output, blood gases, and so forth. Such patients are necessarily in a stable state and safe for the moment. It is of great interest, however, to look at what happens when the system gets closer to the region of instability and to a possible downward spiral to death. Observations of this kind have recently been made in the laboratory of Grassino (personal communication) where conscious dogs, previously instrumented with sonomicrometers, intramuscular electromyograph electrodes, and esophageal and gastric catheters, breathe through a circuit. After a period of relaxed normal breathing, they have a large flow resistance added to both inspiratory and expiratory limbs of their breathing circuit to stimulate acute severe generalized airways obstruction. Data from such an experiment are shown in Figure 22. Once the load is in place, ventilation and oxygen saturation immediately go down, and esophageal pressure swings go up. Gradually over the next 20 min, while regular breathing continues, esophageal pressure swings increase, ventilation increases somewhat, oxygen saturation falls, and arterial $P_{CO_2}$ slowly rises. The centroid EMG falls, suggesting the development of diaphragm fatigue. All of these variables seem to be on their way to leveling out to plateau values after about 30 min. At this point however, $CO_2$ begins to rise very rapidly (Fig. 22a) and there is a sudden and dramatic switch within one or two breaths to an extremely irregular breathing pattern with mixed large and small, long and short breaths (Fig. 22b). After only a few minutes the experimenters have the clinical impression the dog is going to die, and they immediately remove the external resistor. Clearly the control system has passed suddenly from a quasi-stable condition to one with wildly erratic breath-to-breath variations, associated with rapid progression toward death.

Anesthetized dogs with acute severe bronchoconstriction (289) and hypox-


End – tidal $CO_2$ %
10
9
8
7
6
5
4
3
2
0 1000 2000
(a) Time in seconds


Tension–time index
0.0
−0.1
−0.2
−0.3
Pressure ($cmH_2O$)
120
100
80
60
40
20
0
−20
−40
−60
−80
−100
End – tidal $CO_2$ %
13
12
11
10
9
8
7
6
5
4
1800 1900 2000 2100
(b) Time in seconds

emia or external resistive loading and hypoxemia (247), like dogs with cardiogenic shock (248) and infant monkeys with large external resistive loads (249), die because their respiratory control system fails even though there is no muscle fatigue and $P_{CO_2}$ and cardiovascular variables have stabilized on the load. At the point of death there is a slowing of respiratory rate over 15 sec ending in apnea, with little change in magnitude of respiratory effort per breath. This unexpected failure of the integrative control system is the terminal event. New theories must be developed to understand why it occurs.

## XI. Behavior of the Integrated System in COPD

Several kinds of studies give information about behavior of the integrated respiratory control system without trying to isolate the contributions of individual components of the system.

### A. Chronic Stable COPD

*Natural Behavior*

Numerous authors have reported ventilatory measurements on patients with advanced COPD at rest, summarized in Table 4. Minute ventilation is about 10 L/min (slightly lower in those with hypercapnia), above the usual values for normal subjects. Some studies give higher values for resting ventilation than others. This may be explained by the small sample sizes, but could also be related to the deadspace of the apparatus, especially because COPD patients, with high internal deadspace, should be particularly affected by any added deadspace. Respiratory rate averages about 17, and tidal volume about 850 ml. Occlusion pressure is about 3.5, about double the usual values for normal subjects. As COPD progresses and gas exchange deteriorates, ventilation rises progressively to maintain $P_{CO_2}$ normal, and this is achieved almost entirely through an increase in frequency (250).

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**Figure 22** (a) Progression of end-tidal $CO_2$ in an experiment where large inspiratory and expiratory resistances are applied to the airway of a conscious dog after 400 sec of unimpeded breathing (see text). $CO_2$ rises rapidly at first, then more slowly, and is apparently approaching a plateau at about the 1900-sec point when it suddenly begins to rise again, much more rapidly. (b) Breath-by-breath behavior on an expanded time scale for the same experiment shown in (a). From top down, the tracings show tension-time index of the diaphragm, peak expiratory mouth pressure, end-tidal $CO_2$, and end-inspiratory mouth pressure. At 1890 sec, there is a sudden increase in the variance of all the breath-by-breath measurements.

**Table 4** Ventilatory Values for Patients with COPD at Rest

| Ref. Source | *N* | $P_{CO_2}$ | $P_{O_2}$ | FEV%, | FEV/VC | $\dot{V}_E$ | $V_T$ | F | $T_I$ | $T/T_{TOT}$ | $P_{0.1}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Stable Patients* | | | | | | |
| 130 | 12 | 39 | 71 | 50% | 0.46 | 17.8 | 0.91 | 19.4 | 1.13 | 0.37 | 3.7 |
| 267 | 7 | 39 | 74 | 25% | | 10.6 | 0.83 | 14.5 | 1.5 | 0.32 | |
| | 6 | 51 | 59 | 16% | | 9.6 | 0.53 | 18.5 | 0.9 | 0.29 | |
| 120 | 12 | 39 | 68 | | 0.46 | 16.5 | 0.84 | 19 | 1.2 | 0.38 | 3.0 |
| 264 | 17 | 52 | 50 | 4% | 0.50 | 9.6 | 0.57 | 17 | 1.36 | 0.37 | 3.0 |
| 14 | 6 | 41 | 69 | 30% | | 12.1 | 0.70 | 19 | 1.33 | 0.39 | 4.4 |
| | 9 | 55 | 60 | 38% | | 10.8 | 0.48 | 21 | 0.98 | 0.34 | 3.6 |
| 18 | 20 | 38 | 67.4 | 1.73 l | | 10.5 | 0.64 | 17 | | 0.42 | |
| | 85 | 46 | 61.5 | 1.13 l | | 10.5 | 0.63 | 17 | | 0.40 | |
| | 17 | 62 | 51.6 | 0.79 l | | 9.1 | 0.56 | 17 | | 0.37 | |
| 257 | 15 | 40 | 74 | 27% | | 7.6 | 0.46 | 17 | 1.27 | 0.37 | |
| | 15 | 53 | 61 | 22% | | 7.8 | 0.36 | 22 | 1.02 | 0.33 | |
| 259 | 17 | 46 | | | 0.32 | 13.5 | 0.85 | 17 | | | |
| 215 | 8 | 36 | 72 | 38% | | 15.4 | 0.71 | 17 | 1.5 | 0.39 | 2.5 |
| | 7 | 55 | 58 | 22% | | 14.2 | 0.56 | 24 | 0.9 | 0.35 | 1.0 |
| 291 | 63 | | | 42% | 0.46 | 11.6 | 0.62 | 19.8 | 1.2 | 0.35 | 2.8 |
| 232 | 12 | | | 15–49% | | 11.2 | 0.55 | 22 | 1.05 | 0.36 | |
| 250 | 8 | 39 | 68 | 18% | | 10.9 | 0.49 | 23 | 0.94 | 0.35 | |
| | 8 | 52 | 47 | 17% | | 7.6 | 0.33 | 24 | 0.94 | 0.37 | |
| | | | | | *Acute Failure* | | | | | | |
| 92 | | 77 | 123 | | | | 370 | 23 | | | |
| 95 | 20 | 61 | 38 | 25% | 0.39 | 11.4 | 0.38 | 32 | 0.68 | 0.34 | 8.3 |
| 19 | 22 | 65 | 38 | 27% | | 10.2 | 0.34 | 32 | 0.65 | 0.34 | |
| 216 | 14 | 54 | 48 | 26% | | 9.9 | 0.37 | 28 | 0.79 | 0.37 | |

*N* refers to the number of patients in each study. Where there are two or three lines of data for one article they refer to groups of patients with normocapnia and hypercapnia, as in Table 2. Format for $FEV_1$ is the same as in Table 2: % means % of the predicted value, number with a decimal refers to the ratio $FEV_1/VC$, L refers to absolute values in liters. The units for blood gases are mmHg, for $\dot{V}_E$, L/min, for $V_T$, L, for F, $min^{-1}$, for $T_I$, seconds, for $P_{0.1}$, $cmH_2O$.

COPD patients at rest have more activity of neck accessory muscles than normals (251), and more of their inspiratory pressure is attributable to activity of intercostal-accessory muscles and to elastic recoil due to relaxation of expiratory muscles than in normal subjects (16,252,253). These observations indicate that the overall output of the neural respiratory controller is above normal in stable COPD patients at rest. Gorini et al. (14) compared resting normalized diaphragm EMG in six normocapnic and nine hypercapnic (mean 55 mmHg) COPD patients and

found the EMG was greater in the hypercapnic patients, suggesting that respiratory motoneuron output was higher in hypercapnic patients.

Other well-known behaviors of the control system are a tendency to pursed lips breathing, which prevents collapse of airways in expiration and reduces dyspnea (187), and a preference for postures that are known to be advantageous for effectiveness of respiratory muscles and for relief of dyspnea (137,254).

### *Population Studies*

Surveys of populations of COPD patients with a range of resting levels of $P_{CO_2}$ try to correlate the $P_{CO_2}$ with measurements of mechanics or muscle function. In general, variance in the $P_{CO_2}$ that cannot be correlated with the mechanics or muscle measurements is presumed due to variance in behavior of the control system. However, there is always the possibility that the measurements that are applied are not sophisticated enough and may have missed some subtle, but important aspect of mechanics or muscle function.

Lane et al. (255) found that variations in $P_{CO_2}$ over time could be correlated with variations in $FEV_1$ in some individuals among 13 COPD patients, but the relationships were quite different for different patients. In a larger study, Lane and Howell (256) found that $FEV_1$ accounted for only a small part of the variation in $P_{CO_2}$ across patients. The report of Prime and Westlake (75) on 35 patients found some correlation between resting $P_{CO_2}$ and maximum breathing capacity, but the correlation was poor. Sorli et al. (215) compared eight normocapnic and seven hypercapnic COPD patients. The hypercapnic patients had somewhat lower values for VC, $FEV_1$, and $P_{0.1}$ and higher values of RV and FRC/TLC. With respect to control measurements, however, they were identical in $\dot{V}_E$, $P_{0.1}$, $V_T/T_I$, and $f$. The only difference was in tidal volume and in inspiratory time. These authors proposed that the difference between normocapnic and hypercapnic COPD patients was a difference in control of pattern of breathing: that the hypercapnic COPD patients breathed with a lower tidal volume and therefore a worse $V_D/V_T$ ratio. A similar study by Javaheri et al. (257) on 15 normocapnic and 15 hypercapnic patients matched to have equivalent age, height, sex, lung volumes, flow rates, diffusing capacity, and $CO_2$ production found a similar difference between the groups. Hypercapnic patients had lower tidal volumes, higher respiratory rates, and higher measured $V_D/V_T$. Like Sorli et al., these authors found that most of the hypercapnic patients were bronchitic and postulated that bronchial inflammation, by stimulating vagal receptors, might be responsible for the difference in pattern of breathing. On the other hand, Bradley et al. (41) found more rapid shallow breathing in hypoxemic COPD patients compared to normoxemic ones. Among their 20 hypoxemic patients there was no difference in pattern of breathing between the hypercapnic ones and the normocapnic ones. In a

larger study Parot et al. (258) found that patients with $P_{CO_2} > 55$ differed from normocapnic patients mainly in having more rapid shallow breathing. Using noninvasive measurements (inductance plethysmography), Loveridge et al. (250) confirmed that more servere COPD cases tended to have lower tidal volumes and higher frequency, even more so when there was hypoxemia or hypercapnia.

Most of these studies describing differences in pattern of breathing have involved small numbers of patients and are subject to a statistical reservation because multiple statistical tests were done looking for patterns. The findings, though provocative, need to be confirmed. Also, a relationship between rapid shallow breathing and $CO_2$ retention need not be cause and effect. Another explanation may be simply that many of the patients with $CO_2$ retention are getting close to their muscle-mechanical limit or their fatigue threshold, and because of that have limits to their tidal volume and must increase frequency to maintain ventilation.

Previous small population studies have been superseded by the huge work of Begin and Grassino (18), who examined 311 stable COPD patients with a series of sophisticated tests designed to evaluate respiratory muscle reserve as well as mechanical and gas exchange impairment. They found $PaCO_2$ was directly related to lung resistance and inversely to $FEV_1$ and to deadspace expressed as $(1 - V_D/V_T)$. Maximal inspiratory pressure related to lung resistance as $R_L/P_{I_{max}}$ was found to be the best predictor of $P_{CO_2}$. Obesity also made a contribution. A multiple regression equation for $P_{CO_2}$ was developed.

$$Paco_2 = 13.61 + 0.65\ R_L + 0.37El_{dyn} + 6.28\ \text{weight} + 25.38\ V_D/V_T + 90.83\ P_{I_{max}}$$

Altogether these measures of mechanics and muscle strength accounted for only about half of the variance in arterial $P_{CO_2}$, however. It is possible that some of the remaining variance was explained by an unmeasured muscle-mechanical problem, namely the development of intrinsic PEEP. But it seems likely that a substantial amount of variance in $P_{CO_2}$ is due to interindividual differences in control of respiration.

### *Effects of Oxygen Administration*

Administration of oxygen to stable COPD patients causes small increases in $P_{CO_2}$ and has been studied to understand the much larger changes in $Paco_2$ seen when oxygen is given to patients in acute respiratory failure. Sassoon et al. (259) switched their 17 patients back and forth between 15-min periods of air and oxygen breathing. Oxygen produced a rise of $P_{CO_2}$ from a mean of 45.8 to 48.9 mmHg associated with a small fall in ventilation from 13.5 to 12.8 L/min, a decrease in frequency from 16.7 to 15.9 $min^{-1}$, an increase in $V_D/V_T$ from 49

to 53%, and a decrease in $CO_2$ from 284 to 264 ml/min. Only the changes in $P_{CO_2}$ and $V_D/V_T$ were statistically significant. The percent changes in ventilation correlated well with percent changes in $\dot{V}_{CO_2}$ typical of a normally functioning control system and should in this way have tended to stabilize $P_{CO_2}$. The factor that seemed mainly responsible for the rise in $P_{CO_2}$ was therefore the increase in $V_D/V_T$. Since $V_T$ did not change, the rise in $V_D$ was attributed to a shift in $\dot{V}/Q$ ratios, as described previously (260–262). In an older study in which the clinical state (chronic vs. acute) was not clearly stated (75), the rise in $P_{CO_2}$ when oxygen was given correlated with the starting value of $P_{CO_2}$ (263).

### *The Effects of Respiratory Stimulants*

Direct evidence that the degree of carbon dioxide retention is not always the obligatory consequence of muscle or mechanical limitations comes from studies of prolonged use of respiratory stimulants. It was recognized long ago that some COPD patients with $CO_2$ retention are able to reduce their $P_{CO_2}$ quite markedly by voluntary hyperventilation, while others are not. This implies that some patients have some unused ventilatory reserve and presumably could safely increase their level of ventilation in their chronic stable state. Skatrud et al. (264) gave medroxyprogesterone over 4 weeks to 17 patients with chronic hypercapnia (mean $P_{CO_2}$ 51 mmHg) of whom 14 had COPD. Ten patients (including nine of the COPD patients) had a drop of more than 5 mmHg in $PaCO_2$, the mean value going from 51 to 43. Ventilatory response to $CO_2$ did not help in predicting which patients would respond to the drug. On the other hand, all of those who responded, but only one of the COPD patients who did not respond to medroxyprogesterone, were able to lower their $P_{CO_2}$ by voluntary hyperventilation, suggesting that the ability to hyperventilate voluntarily was a useful test of whether the individual patients still had usable ventilatory reserve and would therefore be able to respond to a respiratory stimulant. Morrison and Goldman (265) also found that some patients with hypercapnia could be improved by progesterone, but in their hands this positive response was not predicted by the voluntary hyperventilation test.

### *Attempts to Alter Ventilatory Behavior*

It is sometimes proposed that patients be trained to change their breathing pattern from the natural one governed by the automatic ventilatory controller to one that is supposed to be more advantageous physiologically. A change from rapid shallow breathing to slow deep breathing is advantageous for gas exchange because of an improved deadspace to tidal volume ratio and might perhaps not change the work rate of inspiratory muscles. In fact, however, patients with severe COPD have trouble maintaining a slow deep breathing pattern, become short of breath, and show signs of impending diaphragmatic fatigue due to the higher transdiaphrag-

matic pressure needed to produce each tidal volume (224). Diaphragmatic breathing, which seems to relieve dyspnea in some patients, has recently been shown to decrease the efficiency of respiratory muscles (222). Pursed lips breathing is taught to some COPD patients and performed naturally without instruction by others. The physiological advantages of pursed lips breathing are unclear except for the likelihood that it prevents collapse of pulmonary airways in expiration (187; see Chapter 24). It is possible that patients who do use pursed lip breathing are those whose pulmonary airways tend to collapse in expiration, and that many of those who do not naturally do so are still breathing inside their maximal expiratory flow curves and so have nothing to gain.

To date the results of trying to change the pattern of breathing in these patients are consistent with the idea that the natural pattern chosen by each patient's respiratory controller is in fact close to the optimum one.

#### *Summary*

Together the data can be interpreted to mean that not all chronic stable COPD patients are the same with respect to their breathing control systems. While mechanics and muscle strength are obviously major factors in deciding the level of $CO_2$, some patients seem to have control systems that defend blood gases more tenaciously than others. Indirect evidence to support this view comes from the known wide normal range of ventilatory response to $CO_2$, the tendency for the degree of sensitivity to $CO_2$ and $O_2$ to be inherited, and the finding that $CO_2$ retainers with COPD are more likely than other COPD patients to have relatives with poor responses to $CO_2$ and $O_2$.

### B. Experimental Simulation of Acute Respiratory Failure in COPD

Several studies have been reported in which experimenters made increments to the mechanical load in normal subjects or in patients with moderate to severe COPD, trying to simulate the mechanical effect of the presumed bronchial infection or bronchospasm that is thought to provoke clinical episodes of respiratory failure.

Cherniack and Chodirker (266) attempted to replicate the situation of acute respiratory failure by having normal subjects breath through a high airway resistance, or by making them hypoxemic by breathing a low oxygen gas mixture, or by combining the resistance with hypoxia. Administration of oxygen produced a noticeable drop in minute ventilation in the subjects breathing the hypoxic mixture through a resistor, but not when they were only hypoxic, and the resistor by itself produced no changes in ventilation. These results suggest that breathing through the resistor somehow exaggerated their sensitivity to hypoxia.

Experiments have been done more recently in which patients with moderate to severe COPD have had an extra resistive load imposed on them in both

inspiration and expiration, partially simulating the increase in airways resistance that is presumed to occur in these patients during the acute bronchial infections that precipitate acute respiratory failure. Oliven et al. (130) added resistances of 2.5–30 $cmH_2O/L/sec$ in 12 patients breathing oxygen. One was not able to tolerate a resistance greater than 10, but most could tolerate 15 and two subjects went as far as 30 $cmH_2O/L/sec$. The patients seemed to fall into two groups: some increased $P_{CO_2}$ more markedly with increasing resistance (a rise of more than 6 mmHg with a resistance of 10), and some increased $P_{CO_2}$ rather little (a rise of less than 3 mmHg with a resistance of 10). The ones who increased $P_{CO_2}$ more markedly had lower maximum static inspiratory pressure, and they shifted their breathing pattern to one of lower tidal volume, shorter inspiratory time, and higher frequency. There was only a weak correction between ventilatory response to the loads and the changes in $P_{CO_2}$. In a second study, Oliven et al. (119) induced acute airways obstruction with methacholine in 12 COPD patients. For the group, the drug in its largest dose caused an increase in airways resistance from 3 to 5 cm $H_2O/L/sec$, a rise of 1.5 L in FRC, and a reduction of one-third in maximum inspiratory pressure. Ventilation actually increased slightly as resistance increased, as did occlusion pressure. In spite of that, $P_{CO_2}$ rose, probably because of a shift to higher frequency and lower tidal volume, which correlated with the change in $P_{CO_2}$ ($CO_2$ production was measured and found to increase only slightly, not enough to account for the rise in $P_{CO_2}$.) Baseline airways obstruction was a good predictor of the increase in $P_{CO_2}$ with methacholine but the ventilatory and occlusion pressure responses to $CO_2$ were not. Bronchoconstriction reduced the ventilatory response to $CO_2$. The $P_{0.1}$ response was unchanged in spite of the rise in FRC, which should have decreased $P_{0.1}$. The increase in ventilation after bronchoconstriction could be attributed to stimulation by the rise in $CO_2$. Similar changes in tidal volume and frequency with histamine inhalations were described by Pardy et al. (267), who emphasized that patients who were initially normocapnic and normoxic showed the greatest change in $V_T$ and $f$ with histamine, so that after administration of the drug at the $PC_{20}$ dose these patients breathed in a style very similar to that of the previously hypoxic and hypercapnic patients. The latter groups, who already had rapid shallow breathing, changed their style of breathing much less with the histamine.

### C. Behavior of the System in Acute Failure

#### *Natural Behavior*

A few studies have given some information about the evolution of respiratory variables over the first few days of ARF. Minute ventilation at the time of admission was found to be in the range of 10–12 L/min, similar to the value in a chronic stable state (95), but respiration is about twice as rapid (approximately 32/min) and shallow ($V_T$ approximately 400). Inspiratory flow rate is higher as

well, and correlates with $P_{0.1}$. Occlusion pressure is very high, approximately 8 $cmH_2O$ (95,268). Qualitatively these changes parallel the ones seen in COPD patients given methacholine (119). After a few days, ventilation remains the same, but tidal volume has risen, frequency has fallen, and $P_{CO_2}$ has fallen. Occlusion pressure has also come down to values close to those of COPD patients in a stable state (see Fig. 23).

At the time of admission to hospital it can be assumed that the lung disease itself is worse than it is a few days later when the patient is beginning to recover. Airway resistance is certainly higher, and there is probably more dynamic hyperinflation. It can be expected that the amount of respiratory pressure and motoneuron output on the first day is higher for the same amount of ventilation than several days later, during recovery. The high occlusion pressure fits with this expectation. The measured increase in $P_{0.1}$ may, however, be partly due to phase changes between pressure and flow, or to changes in shape of the output pressure wave that go with the very high resistance, high intrinsic PEEP, hypoxia, and acidosis.

Some patients in acute respiratory failure show a peculiar pattern of chest wall movement that has been called dysynchronous breathing, in which the abdomen after expanding through inspiration has a sharp brief decrease in anteroposterior (AP) diameter in early expiration, then reexpands and goes on to decrease slowly to its end-expiratory value. A more complex pattern is also seen in some cases, where abdominal AP diameter is greatest at end-expiration, drops sharply just as inspiration begins, rises in later inspiration, drops sharply at the beginning of expiration, and then rises again through expiration (268a, 269). These patterns are seen in severely ill patients and are associated with a poor prognosis, a need to use mechanical ventilation, and a reduced chance of survival (269). While the exact interpretation of the chest wall movements remains in doubt, they must indicate unusual recruitment of abdominal expiratory muscles and unusual coordination of expiratory and inspiratory muscles. Similar patterns are not normally seen in chronic stable patients (270–272). Some patients also show a pattern of "respiratory alternans" in which they apparently breathe predominantly with their diaphragm for a period and then switch to breathing more with their intercostal and accessory muscles (273), as if trying to rest one set of muscles and then the other.

### *Effects of the Administration of Oxygen*

From the time of the earliest blood gas measurements it was recognized that many COPD patients in ARF, when given oxygen, would have a rise in $P_{CO_2}$ sometimes so marked as to cause a severe acidosis and $CO_2$ narcosis (274–276). Although $P_{CO_2}$ rises slightly in many patients with stable COPD given oxygen, it rises much more in patients in ARF and when the initial $P_{O_2}$ is low (263,277).

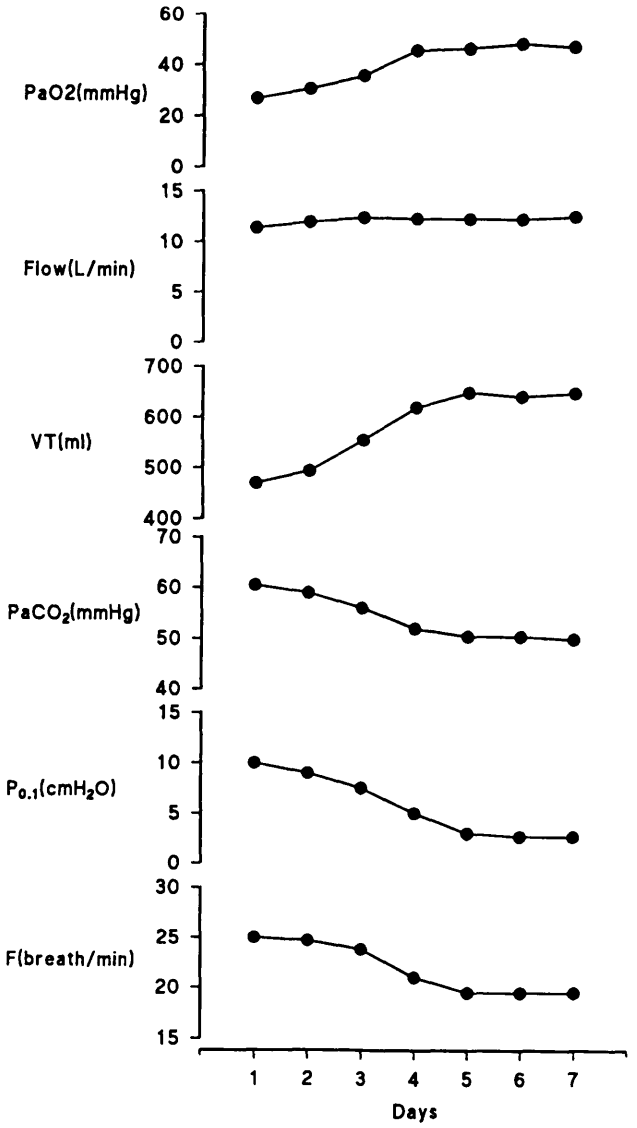


**Figure 23** Progression of respiratory variables in patients with COPD in acute respiratory failure over the first week in hospital. (Modified from Ref. 95.)

It was shown that the rise in $P_{CO_2}$ for a given increase of inspired oxygen was different for different subjects (278) and that in each subject the degree of rise in $CO_2$ with a small increase in inspired oxygen was a good predictor of the degree of further increase in $CO_2$ with larger increases in oxygen. It was recognized that the possible explanations for the rise in $CO_2$ were (1) a decrease in ventilation caused by loss of hyperoxic stimulus, (2) an increase in $V_D/V_T$ caused by a redistribution of $\dot{V}$ and Q with oxygen, (3) the Haldane effect, and (4) an increase in $\dot{V}_{CO_2}$, with the first two expected to be the main factors (279). A possible confounding factor is a decrease in airways resistance reported with administration of oxygen (280).

The Paris study (19), which measured minute ventilation in spontaneously breathing COPD patients in their first days in acute failure, found that ventilation did decrease immediately when oxygen was given, but partially recovered, so that the "steady state" value after 10 or 15 min was only 0.7 L/min less on average than the preoxygen level. The changes in ventilation across subjects did not correlate with the changes in $P_{CO_2}$ that occurred with oxygen administration. Changes in tidal volume-frequency relationships did not explain the discrepancies either. These observations emphasized the potential importance of an oxygen effect on the $V_D/V_T$ ratio in these patients, or possibly on $\dot{V}_{CO_2}$.

If we accept the data of Aubier et al. (19) on the behavior of the average patient with COPD in acute failure and suppose that chemoreceptor drive is indeed determining minute ventilation in these circumstances, then the steady state before oxygen is given is described in Figure 24 by point A, where a metabolic curve for a typical patient in ARF with a typical $V_D/V_T$ of 0.77, a typical $\dot{V}_E$ of 10.2 L/min, and a $P_{CO_2}$ of 65 is drawn. (Despite the discussion in Section IVB, it is not unreasonable to suppose that a patient with marked hypoxemia and an acute respiratory acidosis would indeed by on the upward sloping portion of the $CO_2$ response curve and subject to the analysis requiring that the steady state satisfy both the metabolic curve and a linear controller curve as in Fig. 24a.) A typical slope of the controller curve for this hyperoxic patient is unknown, because the only data available for ventilatory response to hypercapnia have been collected under hyperoxic conditions, but an arbitrary controller curve is drawn through point A with a slope of 0.34, double the slope measured in hyperoxia, and based on the data of Flenley and Millar (63) and Erbland et al. (106) on hyperoxia-hypercapnia interactions in COPD. When oxygen is given, the average patient (19) moves to a point B with a higher $P_{CO_2}$ of 88 mmHg and a lower ventilation of 9.5 L/min. In the new steady state, point B must be on a new metabolic curve, shown as a dashed line shifted to the right because of an increase either in $V_D/V_T$ or in $\dot{V}_{CO_2}$. Data from Tardif et al. (91) indicate that at point B, the average patient has a ventilatory response slope of 0.17 L/min/mmHg as shown by the dashed straight line. In this analysis, the patient has moved from one linear controller curve to another. It is plausible to suppose that this is simply a shift from a normal

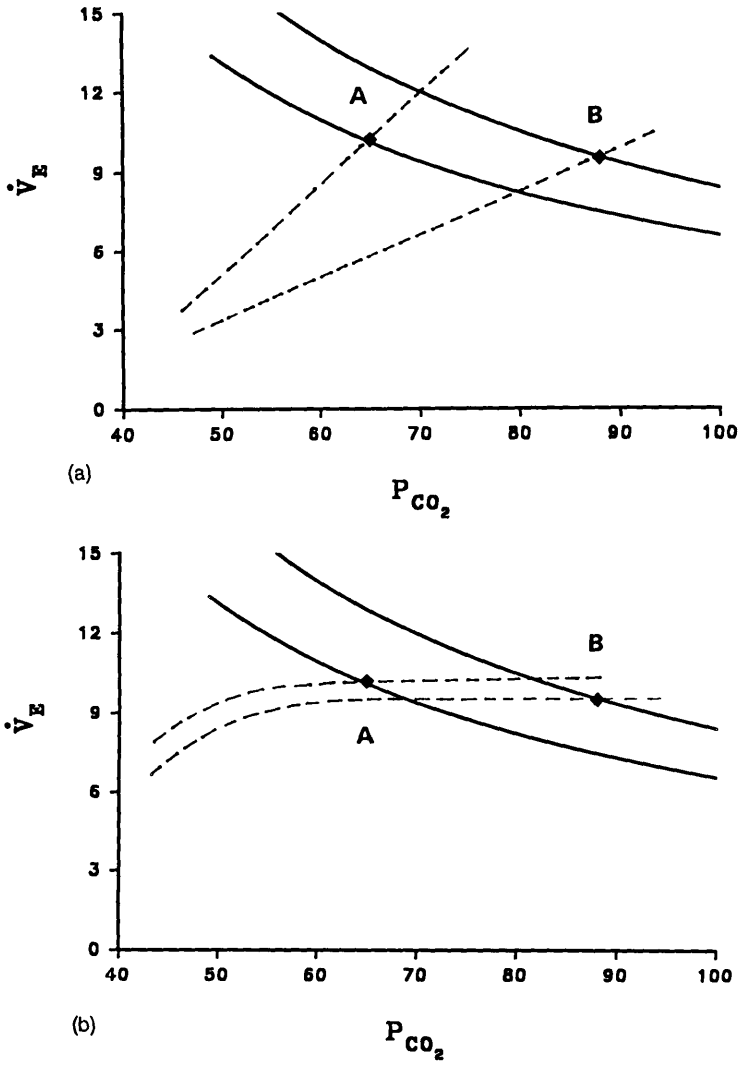


**Figure 24** Effects of oxygen on ventilatory control in acute respiratory failure. (For discussion see text).

hypoxic $CO_2$ response curve to a hyperoxic curve (similar to the curves of Fig. 7a). In that case the chemical control system may be operating quite normally.

Another possibility is diagrammed in Figure 24b. In this case the controller curve, or $CO_2$ response curve, is essentially flat at point A, as was found in some patients of Tardif et al., and hypoxic ventilatory response is negligible. The patient does not increase ventilation at all when $CO_2$ rises, and the new steady state with the same ventilation as before has a higher $CO_2$ because of the shift to the new metabolic curve. The curve might be flat because of impaired sensitivity to the brainstem $CO_2$ or because the system is close to maximum sustainable ventilation and has an absolute mechanical limitation to ventilation or a very strong feedback system (from respiratory muscles, for example) preventing further increases in respiratory motor output.

The wide range of measured ventilatory responses to hypoxia and $CO_2$ in COPD patients and the observed variations between individuals in the importance of other, interacting control systems allow many possible interpretations of this behavior of a typical patient and many variations of the theme of this analysis in atypical patients. A few patients do hypoventilate substantially when given oxygen and may be developing hypercapnia mainly through hyperoxia-induced decrease in respiratory center output.

### *Effects of Respiratory Stimulants*

Respiratory stimulants were introduced to the treatment of acute respiratory failure of COPD to try to increase ventilation, improve acidosis, and avoid the use of mechanical ventilators. The hypothesis that justifies this procedure is that some or all patients in ARF of COPD have respiratory control systems that are not responding optimally for survival and are failing to activate respiratory muscles as completely as they could usefully and safely be activated. (See Chapter 23.)

The one controlled trial of this approach (281) began a steady infusion of doxapram or placebo saline before supplementary oxygen was given and maintained the infusion for 2 hr in experimental and control cases of COPD in acute failure. As shown in Figure 25, the patients in the treatment group maintained their $P_{CO_2}$ constant in spite of administration of oxygen and had higher $P_{O_2}$ and lower $[H^+]$ than the control group, who had a mean rise of 7 mmHg in $P_{CO_2}$. There were no bad side effects of the doxapram at the time, and the procedure was well tolerated by the patients. The authors were cautious about making a clinical recommendation based on the results, particularly because in the follow-up two of the patients in the treated group died, and doxapram has not been widely used since then. Recently the Edinburgh group (282) has reported a prospective series of 139 episodes of COPD patients in ARF among whom they routinely introduced doxapram when pH fell below 7.26 and continued the infusion for 24 hr and longer if pH remained low, or until mechanical ventilation became necessary. Of the 27

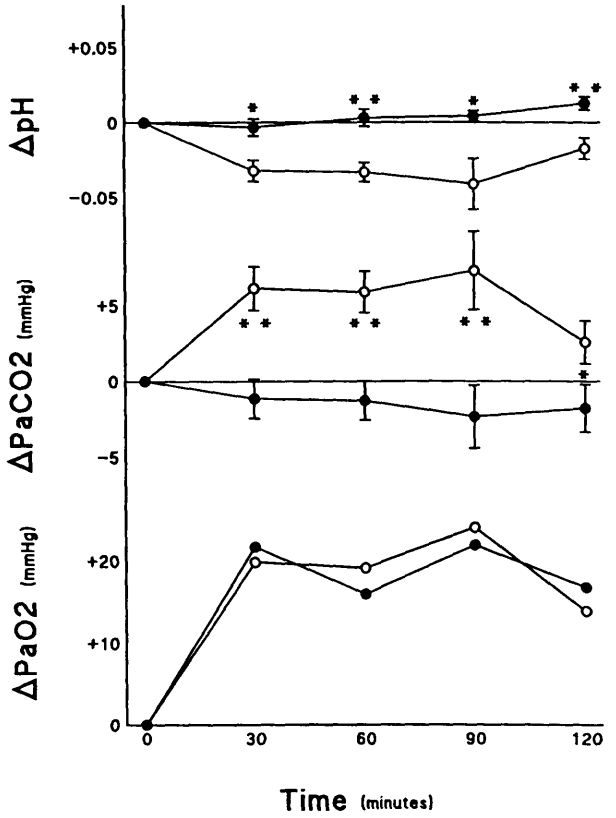


**Figure 25** Results of infusion of doxapram in acute respiratory failure. (Modified from Ref. 281.)

episodes where doxapram was used according to these criteria, pH rose above 7.26 within 24 hr in 23 patients, all of whom survived. Mortality was 30% overall among those who were given doxapram, but the criteria for its use made sure it was given only in the more severe cases. It is not possible to ascertain whether the use of doxapram gave an overall survival benefit to this group of patients, but the number of patients that had to be ventilated (four) was low.

## XII. Conclusions

The ventilatory control system in COPD in ARF may be in, effect, more complex than it is in normal subjects or even in stable COPD because of the increased

importance of feedback systems for muscle protection, of cardiovascular-respiratory interactions, and of sensation and emotion. Analysis of the system is very difficult, and simplistic hypotheses need to be regarded with skepticism. There is no particular reason to expect the control system to choose the optimal ventilation, pattern of breathing, lung volume, and chest wall configuration for survival; on the other hand, it is not clear when interventions to alter the behavior of the ventilatory controller would be advantageous. In some cases, the addition of a respiratory stimulant to counter the drop in alveolar ventilation that occurs with administration of oxygen seems to be safe and beneficial, but this may not always be true. Substantial differences between individuals in effectiveness of components of the control system mean that treatment directed at altering behavior of the controller should ideally be based on assessment of the state of the control system in the individual patient. We do not yet have the theoretical or practical tools to make such assessments.

New experimental evidence on breath-to-breath stability of patterns of breathing suggests strongly that patients in acute respiratory failure may die because of shutdown or disorganized, chaotic behavior of the ventilatory controller before any of the fundamental homeostatic variables such as oxygen delivery, hydrogen ion, or respiratory muscle strength reach a fatal level. Study of behavior of the controller as it nears its limits may soon provide new insights into the optimal operation and the limitations and the mechanisms for failure of the vital integrative mechanism.

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# 8

# Gas Exchange During Acute Respiratory Failure in Patients with Chronic Obstructive Pulmonary Disease

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A main feature of acute respiratory failure (ARF) in patients with chronic obstructive pulmonary disease (COPD) is the rapid worsening of gas exchange leading to a decrease in $Pa_{O_2}$, an increase in $Pa_{CO_2}$, and a decrease in arterial pH. In this chapter the different causes of ARF and their consequences on gas exchange will be schematically described. However, first a description of gas exchange alterations in stable COPD seems necessary, as the initial status of the patient could be a key point in the decompensation process. Causes of ARF and their consequences on gas exchange will then be analyzed, and finally the effects of therapies will be described.

## I. Gas Exchange in Stable COPD Patients

### A. Determinants of Hypoxemia

Hypoxemia could be due to one or a combination of several factors: hypoventilation, ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch (including right-to-left shunt), diffusion alteration, and low mixed venous $P_{O_2}$ ($P\bar{v}_{O_2}$). Among these factors, $\dot{V}/\dot{Q}$ heterogeneity seems to be the major determinant of hypoxemia (1,2). Hypoxemia due to alveolar hypoventilation is associated with hypercapnia, however, the

reverse may not be true; gas exchange may worsen without alteration in ventilation. More details on this condition will be given later. When $Pa_{O_2}$ predicted from the recovered distribution of $\dot{V}/\dot{Q}$, using the multiple inert gas technique (MIGT), is close to measured $Pa_{O_2}$, diffusion alterations in the membrane and the gas phase, at least in stable rest state, seem negligible. A low $P\bar{v}_{O_2}$ could enhance hypoxemia whatever its cause. A low hemoglobin concentration, a low cardiac output, or a high $O_2$ consumption, other conditions being constant, can each decrease $P\bar{v}_{O_2}$ and then $Pa_{O_2}$. An increase in the overall $\dot{V}/\dot{Q}$ (Fig. 1) is needed to keep $Pa_{O_2}$ stable in these conditions.

### *Heterogeneity of V/Q Distribution*

Following the classification by Wagner (1), three types of $\dot{V}$ and $\dot{Q}$ distribution heterogeneities as a function of $\dot{V}/\dot{Q}$ can be distinguished. The H type, which seems to be the most common, has an abnormal fraction of ventilation distributed in high $\dot{V}/\dot{Q}$, the L type has a mode of perfusion in low $\dot{V}/\dot{Q}$, and the other patients have both abnormalities (HL pattern). The frequency of these distributions in the study of Marthan et al. are 50, 21, and 29%, respectively (2). Patients with the H pattern are less hypoxemic at rest than L and HL patients ($63 \pm 10$, $57 \pm 10$, $52 \pm 8$

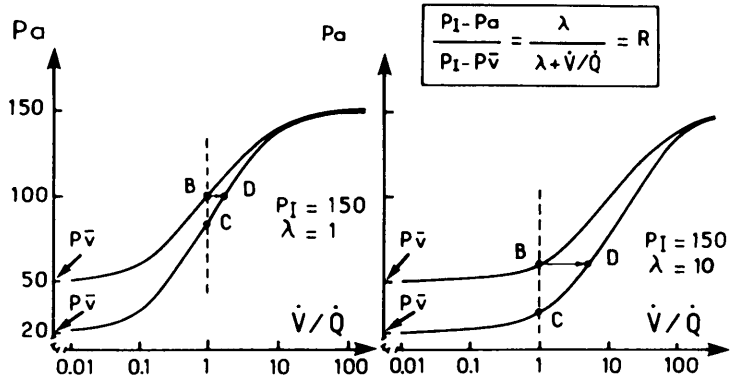


**Figure 1** Plot of $Pa_{O_2}$ (mmHg) against $\dot{V}/\dot{Q}$ in a single alveolar unit assuming that $O_2$ has either a low capacitance (left panel) or a high capacitance (right panel). When $P\bar{v}_{O_2}$ decreases from 50 to 20 mmHg (B to C), if no change in $\dot{V}/\dot{Q}$ figure occurs, $Pa_{O_2}$ would decrease. To keep $Pa_{O_2}$ constant needs an increase in $\dot{V}/\dot{Q}$ (B to D). The capacitance or effective solubility of the blood for $O_2$ is proportional to $\lambda$. In vivo $\lambda$ value decreases with $PO_2$ and increases with Hb concentration and the affinity of Hb for $O_2$. As indicated in the enclosed formula the main determinant of $Pa_{O_2}$ are $PI_{O_2}$, $P\bar{v}_{O_2}$, $\lambda O_2$ and $\dot{V}/\dot{Q}$ (After Guenard) (137).

mmHg, respectively) but have more wasted ventilation. Wagner et al. found a correlation between the clinical type A of Burrows (3) and the distribution pattern H (7/8 patients), although B patients were not found to have a particular distribution pattern. In the work of Marthan et al., the correlation between Burrows' classification and the distribution patterns was not clear-cut. The five patients with suspected pure emphysema, who were all of clinical type A, had H pattern in two cases and HL in three cases, and the 29 patients with a history of chronic bronchitis were H = 52%, HL = 27.5%, and L = 20.5%. Therefore it seems that no close correlation can be made between the clinical type of patient and their distributions. The occurrence of a true shunt (>5%) in these patients is negligible in both Marthan et al. (2) and Wagner (1) studies, as well as in the 16 patients studied by Barany et al. (4). However, a high shunt fraction in stable COPD could be due to associated liver or cardiac disease. Cirrhosis can be complicated with intrapulmonary shunts (5) due to nonventilated neocapillaries. Pulmonary hypertension, by increasing right atrial pressure, could reopen the foramen ovale, leading to a right-to-left shunt (6).

In fact, the distribution patterns depend on the relative alterations in ventilation and perfusion. An H-pattern lung may be made either of many poorly ventilated but less perfused areas or from a few highly ventilated and less perfused areas, and conversely for an L-pattern lung. The MIGT has the inherent drawback of revealing nothing about the amount of lung volume involved in the abnormal mode of ventilation or perfusion, as well as nothing about the amount of lung excluded from any perfusion or ventilation. Thus, several reasons might explain the low observed correlations between clinical findings and the distribution patterns recovered from the inert gas technique. Ventilation and perfusion scintigraphies give topographic indices of $\dot{V}/\dot{Q}$ distribution. Furthermore, unperfused and unventilated areas can be detected. However, the resolution of scintigraphies of $\dot{V}/\dot{Q}$ figures is low, therefore heterogeneities within the lobular size cannot be detected.

The H, L, and HL patterns described above may suggest structural alterations, even if few structure-function correlation studies have been performed apart from two studies, one using positron emission tomography correlating negatively pulmonary density to $\dot{V}/\dot{Q}$ (7), the other correlating morphological findings, recovered from surgically removed lung specimens, to gas-exchange studies (8). In this last study concerning mild COPD patients, the inflammation score was correlated to the slope of the single breath nitrogen washout, the percent TLCO decrease, and the heterogeneity of ventilation. The emphysema score was correlated to the percent decrease in TLCO and $Pao_2$, the increases in $(A\text{-}a)Do_2$, and both $\dot{Q}$ and $\dot{V}$ heterogeneities. Because the patients had mild COPD, this study did not allow correlating the patterns of $\dot{V}/\dot{Q}$ with morphological findings, however, the study indicated that emphysema and inflammation are complementary factors that combine in impairing $\dot{V}$ and $\dot{Q}$ distributions.

Patients with the H pattern are suspected to have low perfusion in many areas of the lungs, which could mean that pulmonary vessels are either clogged or destroyed. These two hypotheses are both confirmed by pathological findings. Thrombosis in pulmonary vessels was described in 1941 by Savacool and Charr (9). In patients who died from COPD, the extent of thrombosis estimated from postmortem lung angiography reached 80% in the study of Bignon et al. (10). The destruction of pulmonary vessels in the course of the centrilobular or panacinar emphysema is well known and the occurrence of emphysema in COPD is very high in all cases after the age of 60 studied by Snider (11). Recent findings supported by computed tomography (CT) scan imaging rather suggest that emphysematous lesions are nearly constant in smokers, whatever their age (12). Apart from thrombosis or destruction, two other factors could contribute to underperfusion: loss of elastic recoil on wall vessels and vasoconstriction (13).

Patients with the L pattern have low ventilation in many areas of the lung, suggesting the presence of physiological obstruction more or less scattered throughout the airways increasing the heterogeneity of ventilation. The narrowing of airway caliber could be due to a combination of several factors: secretion, mucus hyperplasia, muscular hypertrophy, smooth muscle hyperreactivity, and loss of elastic recoil. Changes in the structure of the parenchyma, apart from bronchi, could also be a factor affecting ventilation. The structure of the lobules destroyed by the emphysema process can lead either to a high compliance zone, which is slow to empty, or to a low compliance zone, which is hard to ventilate. In smokers, centrilobular and panlobular lesions may both be present (14). The former lesion reduces ventilation by increasing bronchiolar obstruction and reducing compliance as the latter reduces ventilation by increasing compliance.

Considering the fact that the heterogeneities of the distributions of $\dot{V}$ and $\dot{Q}$ are both increased in COPD, it could be that a loss of control of these distributions contributes to the widening of distributions. There are at least two arguments against this concept in COPD patients: the effects of anesthesia and those of almitrine. Many anesthetic drugs are powerful smooth muscle relaxant substances, whereas others are contractant on both vessels (15) and bronchi (16). Therefore, if relaxant drugs widened the distributions of $\dot{V}$ and $\dot{Q}$, it would prove that the control of smooth muscle contraction is still effective in reducing the heterogeneities. Dueck et al. (17) reported the effect of anesthesia with halothane and $H_2O$ in 16 patients with mild or moderate degrees of $\dot{V}$ and $\dot{Q}$ heterogeneities. After anesthesia all of the distributions worsened—either high true shunts (23% of cardiac output) or perfusion in low V/Q units (32% of cardiac output) appeared. Almitrine, which is thought to enhance hypoxic vasoconstriction, increases $Pao_2$ by reducing the heterogeneity of perfusion (18). Thus, during COPD, the control of the distributions of $\dot{V}$ and $\dot{Q}$, even if not optimal, is still present. Intraairway $Pao_2$, $Paco_2$ and blood pH are factors that control the constriction of bronchial smooth muscle. Hypocapnia can induce a bronchoconstriction, which has been

well documented during the early phase of pulmonary embolism or pulmonary arterial occlusion (19), however, its effect is transient and can be so weak that pulmonary embolism leads in most cases to high $\dot{V}/\dot{Q}$ units easily detected by lung $\dot{V}$ and $\dot{Q}$ scintigraphies (20). Hypoxia induced by low $F_{IO_2}$ has no effect on airway function in humans unless stimulated by nonspecific factors like methacholine (21,22). In sheep this effect has been attributed to the stimulation of carotid chemoreceptors (23). Blood acidosis increases the tonus of the tracheal smooth muscle as well as the response to acetylcholine (24,25) therefore pH should have no effect on the optimization of the distribution of ventilation, other than by potentiating the action of some regional factors. Therefore, both hypoxia and acidosis are potent factors of airway obstruction, effects that are worthy of consideration during ARF.

Alveolar hypoxia has a direct vasoconstrictor effect whatever the value of $P\bar{v}O_2$ (26), suggesting that distal muscular arterioles receive some oxygen from the alveolar spaces. The extensive muscularization of distal arterioles in patients with hypoxemia should enhance the sensitivity to alveolar hypoxia. Indeed some patients with hypoxemia and pulmonary arterial hypertension are very sensitive to 1-day oxygen-inhalation therapy (27). However, muscular hypertrophy can itself be a factor of obstruction to blood flow. People living at high altitude who have such hypertrophy do not decrease their pulmonary arterial pressure when breathing oxygen (28). Low $P\bar{v}O_2$ is also a vasoconstrictor factor, acting on all arterioles in the lungs. Therefore, $P\bar{v}O_2$ cannot be a factor of adaptation to regional blood flow condition unless an interaction between a low $P\bar{v}O_2$ and local alveolar hypoxia exists. This interaction has been clearly established and quantified, the effect of alveolar hypoxia being determinant (26,29). Another possible interaction is with the acid-base status of the blood. Metabolic acidosis increases the vascular tone, and alkalosis has the reverse effect (30). In animal experiments, the interaction between $P_{O_2}$ and pH appears effective as, in the same low $F_{IO_2}$ breathing condition, $Pa_{O_2}$ is higher in metabolic acidosis than metabolic alkalosis. This effect is due to the shift of the oxyhemoglobin dissociation curve (ODC) to the right with acidosis on the one hand, while it may also be due to less heterogeneity in the distribution of Q (31). The effects of respiratory acidosis and alkalosis are more controversial. It seems that the effect of pH is counterbalanced by a pH-unrelated dilating effect of $CO_2$ on pulmonary vessels (32).

### *The Oxyhemoglobin Dissociation Curve and Hypoxemia*

An increase in the hemoglobin affinity for oxygen, i.e., a shift of the ODC to the left, even of a few mmHg leads to a decrease in $Pa_{O_2}$, other conditions being constant. Two factors could explain this effect: the capacitance of the blood for $O_2$ and the curvature of the ODC. The capacitance, or effective solubility of $O_2$ in the blood, $\alpha O_2$, is the volume of $O_2$ that can be accepted by the blood for a small

increase in $Po_2$, i.e., the capacitance is proportional to the slope of ODC expressed as the concentration of $O_2$ as a function of $Po_2$. Therefore, the capacitance is a function of both the affinity of Hb for $O_2$ and the concentration of Hb (Fig. 1). The relationship between the arterial pressure of a gas and its partition coefficient, $\lambda$, the product of its solubility ($\alpha$) by barometric pressure, is for an inert gas (33);

$$\frac{PI - Pa}{PI - P\bar{v}} = \frac{\lambda}{\lambda + \dot{V}/\dot{Q}} \quad (1)$$

Unlike inert gases for which $\lambda$ is a constant, $\lambda$ for $O_2$ is a function of $Pao_2$, $P_{50}$, and Hb concentration. Therefore, other conditions being constant, a decrease in $\lambda O_2$, increases $Pao_2$. The curvature of the ODC is also a determinant of $Pao_2$ as, for a given arterial saturation ($Sao_2$), $Pao_2$ is lower when this curvature is greater than normal. For example, if $Sao_2 = 86\%$, $Pao_2 = 72$ mmHg for pH 7.1 (right shift of the ODC) and 44 mmHg at pH 7.6 (left shift). However, as far as the transfer of $O_2$, i.e., the $O_2$ concentration difference between arterial and venous blood ($Cao_2 - C\bar{v}o_2$) is concerned, the effect of the capacitance is more important than the effect of the curvature (34).

For a given set of $Pao_2 - P\bar{v}o_2$, there is a value of $P_{50}$ for which the difference $Cao_2 - C\bar{v}o_2$ is maximal, this $P_{50}$ figure is said to be optimal as the transfer of oxygen to the tissue can be maximal. According to the simple analysis of Sold (35) and Willford et al. (36), $P_{50opt} = (Pao_2 \times P\bar{v}o_2)^{1/2}$, i.e., $P_{50opt}$ value is always between $P\bar{v}o_2$ and $Pao_2$ values, as, in most COPD patients, $P\bar{v}o_2$ is above normal $P_{50}$ (27 mmHg). Figure 2 relates $Sao_2 - S\bar{v}o_2$ ($\Delta So_2$), $Pao_2$ and $P_{50opt}$. Nearly all patients with stable COPD have sets of $Pao_2 - \Delta So_2$ which would need a higher than normal $P_{50opt}$. In the work of Mithoefer et al. (37), 10 out of 55 patients (18%) had $P\bar{v}o_2$ lower than 27 mmHg, only 2 patients had $P_{50opt}$ lower than 27 mmHg, and the remaining had higher values. For example, a patient with $Pao_2 = 55$ mmHg and $P\bar{v}o_2 = 33$ mmHg has a $P_{50opt}$ of 42.6 mmHg, a figure that is never spontaneously observed and would need experimental manipulation to be obtained (38). In the steady state of COPD, several factors could alter $P_{50}$, including hypoxemia, $Hb_{CO}$, chronic acid-base disturbance, and anemia (or polycythemia). Hypoxemia is known to increase $P_{50}$ by means of an increase in the 2-3 DPG red blood cell concentration (39,40), at least in acute condition. In stable COPD patients the effect is less striking—the scatter of $P_{50}$ is greater than in the healthy population (41,42). In the saturation range above 50%, a right shift is only seen in ex-smokers or nonsmokers, and a left shift is seen in smokers. In the low saturation range, Clerbaux described a left shift of the ODC in patients with hypercapnia (43). This shift could be considered to be well adapted to severe hypoxemia.

The left shift of the ODC curve due to $Hb_{CO}$ was 0.4 mmHg per percent increase in $Hb_{CO}$ according to Clerbaux (43), 0.3 mmHg according to Collier (44), but the change in $P_{50}$ was not linear according to Okada et al. (45). Apart from

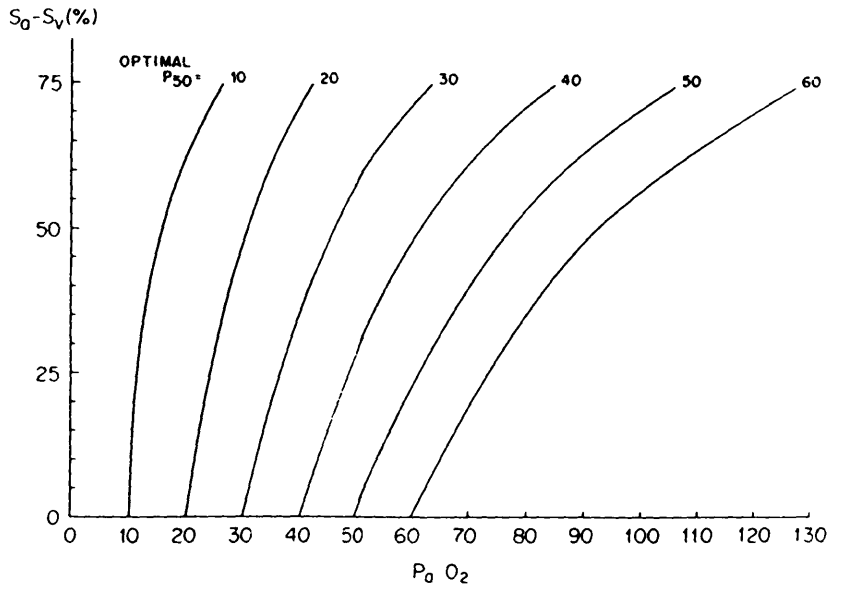


**Figure 2** Arterio-venous $O_2$ saturation difference $(Sa\text{-}S\bar{v})O_2$ as function of $PaO_2$ for different values of the optimal P50. Note that the normal P50 (27 mmHg) is optimal when $PaO_2$ = 30 mmHg for a normal $(Sa\text{-}S\bar{v})O_2$ value i.e. 25%. As far as $O_2$ transport is concerned a lower affinity of Hb for $O_2$ would be needed for most COPD patients (After Willford et al.) (36).

hypoxemia and $Hb_{CO}$, the scatter of $P_{50}$ in COPD patients could also be due to acid-base disturbances following the effects of drugs—mainly diuretics.

Alkalosis shifts the ODC curve to the left and worsens $O_2$ exchange in patients with mild hypoxemia as acidosis shifts the curve to the right and improves $O_2$ exchange. It is worth noting that these effects on gas exchange can be enhanced by the sensitivity of the pulmonary vasculature to the acid-base status (see Sec. I.A).

Anemia and, more frequently, polycythemia are often observed in COPD patients. Anemia is associated with an increase in 2-3 DPG concentration per mass of hemoglobin (46,47) shifting the ODC to the right, an effect that could improve $O_2$ exchange. The specific effect of polycythemia is less clear. At high altitude, hypoxic hypoxia-induced polycythemia in healthy subjects does not significantly shift the ODC curve (48). Therefore, alterations in $P_{50}$ in polycythemic patients are more likely to be due to added disturbances like hypercapnia, severe hypoxia, carboxyhemoglobin, and acid-base disturbances. In most cases, alterations in $\lambda O_2$ and $P\bar{v}O_2$ due to the increased Hb concentration play more determinant roles in gas

exchange than the observed shifts of the ODC, which in any case remain in a narrow range even if greater than in healthy subjects. If cardiac blood flow is kept constant, anemia would reduce $Pa_{O_2}$ slightly, and polycythemia would increase $Pa_{O_2}$, the alterations of $P\bar{v}_{O_2}$ being more determinant than those of $\lambda O_2$ (34,49). However, anemia and polycythemia are often associated with opposite alterations in cardiac output, which by reducing the alterations in $P\bar{v}_{O_2}$ would decrease or even reverse the alterations in $Pa_{O_2}$.

### B. Determinants of Capnia

#### *Hypercapnia and Normocapnia*

Whereas hypoxemia is nearly constant in COPD patients (if not at rest at least during exercise), hypercapnia is less common. In patients with chronic respiratory failure, i.e., with hypoxemia at rest, the occurrence of hypercapnia was reported to be 35% (19/55) (37).

The lack of hypercapnia in most COPD patients could be related to several factors: the small physiological difference between $P\bar{v}_{CO_2}$ and $Pa_{CO_2}$, the need for a great heterogeneity and the distributions of $\dot{V}$ and $\dot{Q}$ to increase $Pa_{CO_2}$, and the sensitivity of the respiratory centers to $CO_2$ and pH, which could be potentiated by hypoxia and the existence of a sufficient ventilatory reserve.

In a simple two-compartment model of the lung (one compartment "ideal," the other unperfused):

$$Pa_{CO_2} = \frac{K \times \dot{V}_{CO_2}}{[\dot{V}_E(1 - V_D/V_T)]} \tag{2}$$

where $\dot{V}_{CO_2}$ is the metabolic production of $CO_2$ and $V_D/V_T$ is the "physiological" dead space. Therefore, variation in $Pa_{CO_2}$ could be due either to $\dot{V}_{CO_2}$ (metabolic disturbance), $\dot{V}_E$ (ventilatory disturbance), or $V_D/V_T$ (distribution disturbance). An increase in $Pa_{CO_2}$, $dPa_{CO_2}$, could be related to these three disturbances:

$$\frac{dPa_{CO_2}}{Pa_{CO_2}} = \frac{d\dot{V}_{CO_2}}{\dot{V}_{CO_2}} - \frac{d\dot{V}_E}{\dot{V}_E} + \frac{d(V_D/V_T)}{V_D/V_T} \tag{3}$$

where $Pa_{CO_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$, and $V_D/V_T$ are the initial values of the parameters and the d values are the differences between the final and the initial values of the parameters provided that these differences are relatively small (50).

#### *Disturbance in the Distribution of $\dot{V}/\dot{Q}$*

$Pa_{CO_2}$, in a single compartment of the lung, depends on the partition coefficient for $CO_2$ ($\lambda CO_2$), the $\dot{V}/\dot{Q}$ ratio, and $P\bar{v}_{CO_2}$. At rest normal $P\bar{v}_{CO_2}$ is close to normal $Pa_{CO_2}$, about 45 and 40 mmHg, respectively, as the difference for $P_{O_2}$ is greater

than 40 and 80, respectively. Therefore, a great heterogeneity in the distribution of $\dot{V}/\dot{Q}$ ($\sigma$) is required to impede $CO_2$ excretion and to raise $Paco_2$ and $P\bar{v}co_2$. Keeping total ventilation and cardiac blood flow constant, a progressive increase in $\sigma$ is followed by a nearly linear fall in $Pao_2$, as $Paco_2$ rises in a curvilinear fashion, slightly for low $\sigma$ values and sharply when high $\sigma$ values are reached (Fig. 3) (49). Thus hypercapnia in this simulated situation is not related to hypoventilation but to the degree of heterogeneity of the distribution.

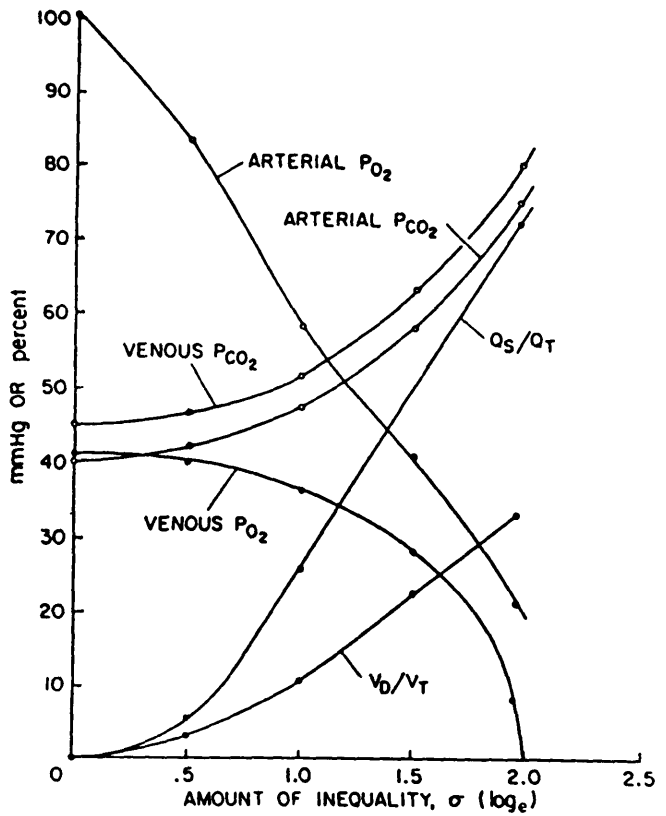


**Figure 3** Alteration in arterial and venous $Po_2$ and $Pco_2$ following an increase in the heterogeneity of $\dot{V}/\dot{Q}$ ($\sigma$), assuming that both ventilation and cardiac output are constant. $Pao_2$ decreases nearly linearly with $\sigma$, as $Paco_2$ increases slightly between $\sigma = 0$ and $\sigma = 1$ and more steadily over 1. A figure of 1 for $\sigma$ fits the degree of heterogeneity often observed in COPD patients (After West) (49).

### *Disturbance in Overall Ventilation*

For a given heterogeneity of the distribution of $\dot{V}/\dot{Q}$, a decrease in overall alveolar ventilation decreases all $\dot{V}/\dot{Q}$ values leading to hypoxemia, and hypercapnia, as an increase in alveolar ventilation, by increasing $V_T$, f, or even decreasing the series dead space by flushing its content at the end of expiration, improves blood gases (51). However, hypoventilation is not easy to isolate from the other causes of hypercapnia as it needs the simultaneous measurements of three out of four parameters of Eq. (3). Nevertheless, hypoventilation could occur in some patients and some circumstances, such as sleep (52), $O_2$ breathing, use of sedative drugs, anesthesia, or respiratory muscle fatigue. Because Eq. (2) is hyperbolic, small alterations in either $\dot{V}_E$ or/and $V_D/V_T$ would alter $Paco_2$ greatly.

As suggested by West (53), the concept of hypoventilation is misleading in the presence of hypercapnia if no measurement of ventilation is available, as hypercapnia can also be due to heterogeneity in $\dot{V}/\dot{Q}$ distribution. However, the concept of hypoventilation has two different meanings: (1) taking only the gas-exchange process into account, in which case hypercapnia may result either from a decrease in ventilation or from the heterogeneity of $\dot{V}/\dot{Q}$ distribution, or (2) taking only the regulation of respiration into account. In this latter sense, $Paco_2$ regulation is the aim of the regulatory system, and if $Paco_2$ is increased, alveolar ventilation is decreased even if its value is higher than normal. Both concepts are interesting but need to be strengthened by useful data telling us something about the "sensitivity" to $CO_2$ drive as well as something about ventilation and the heterogeneity of $\dot{V}/\dot{Q}$.

The ability of the ventilatory system to increase its ventilation in response to $CO_2$ is limited by the power of respiratory muscles and the impedance of the whole chest-lung. When the ventilatory responses to both $CO_2$ and $O_2$ are expressed as a fraction of the maximum voluntary ventilation, much of the difference between normal subjects and most COPD patients disappears, suggesting indeed an adaptation of the $CO_2$ regulatory system to patient lung mechanics (54). Some patients are able to sustain high voluntary ventilation, while some cannot. The former are said to have a good ventilatory reserve (55), whereas the latter might not be able to cope with ARF and should accept an increase in $Paco_2$. However, there is no general rule, and some patients who could increase their ventilation to be normocapnic do not.

### *Disturbance in Metabolic Rate*

An increase in $\dot{V}co_2$ due to muscular activity, either respiratory or not, should be compensated for by an increase in ventilation. In order to reduce this demand, the patient, consciously or not, will reduce his or her general activity in order to minimize the need to ventilate. This behavior could result in positive feedback: the

less the respiratory activity, the less its increase, which would increase the dependency of the patient on family members and medicine.

In healthy subjects the heterogeneities of $\dot{V}$ and $\dot{Q}$ increase with exercise (56), requiring a greater increase in ventilation than cardiac output to keep $Pa_{O_2}$ and $Pa_{CO_2}$ in normal ranges. However, patients with severe COPD are often only able to perform moderate levels of physical activity. In these conditions the distributions of $\dot{V}$ and $\dot{Q}$ remain unchanged (57) or $\dot{V}$ distribution might improve (58). Nevertheless, the increase in $P\bar{v}_{CO_2}$, like the decrease in $P\bar{v}_{O_2}$ (Fig. 1), necessitates higher V/Q values to keep the arterial blood gas values in nearly constant ranges; if not, $Pa_{O_2}$ would fall and $Pa_{CO_2}$ would rise.

#### *Other Disturbances*

An increase in $Pa_{O_2}$ by releasing the $CO_2$ stored on hemoglobin increases blood $P_{CO_2}$. This Haldane effect is transient and should have only slight effects on the daily life of COPD patients. The main occurrence of a significant Haldane effect would be seen when a severely hypoxemic patient (COPD patient with ARF) is given $O_2$—$Pa_{CO_2}$ could rise by several mmHg (59). Another potent cause of hypercapnia is the increase in $P\bar{v}_{CO_2}$ following a decrease in cardiac output. However, in steady COPD patients the cardiac output is usually considered to be normal or near normal (60).

## II. Causes of ARF and Effects on Gas Exchange

### A. Oversecretion and Infection

Chronic bronchitis is defined by recurrent episodes of broncho-pulmonary infections fitting type B patients according to the classification of Burrows (3) combining a long history of coughing with sometimes purulent expectoration, hypoxemia, $CO_2$ retention, congestive lung fields on chest x-ray, and sometimes cor pulmonale. Intraairway plugging is a cause of ventilation heterogeneity and even of true intrapulmonary shunt when the obstruction of bronchi with sputum is total. The role of coughing in keeping airways open is essential, as is the role of the physiotherapist in helping the patient to accomplish this tiring task. Figure 4 illustrates the case of a patient of HL type recovering from an ARF episode but still secretant. The distribution of $\dot{V}$ and $\dot{Q}$ were measured with the inert gas method in a steady state early in the morning and then later once the patient had coughed and expectorated quite a bit. The effect of the expectoration on $\dot{Q}$ distribution was clear: the blood flow passing through the initial shunt was shifted to a less hypoxemic $\dot{V}/\dot{Q}$ mode (61).

Another related effect of infection is fever, which affects both ODC and metabolism. The increase in blood temperature lowers the affinity of the hemo-

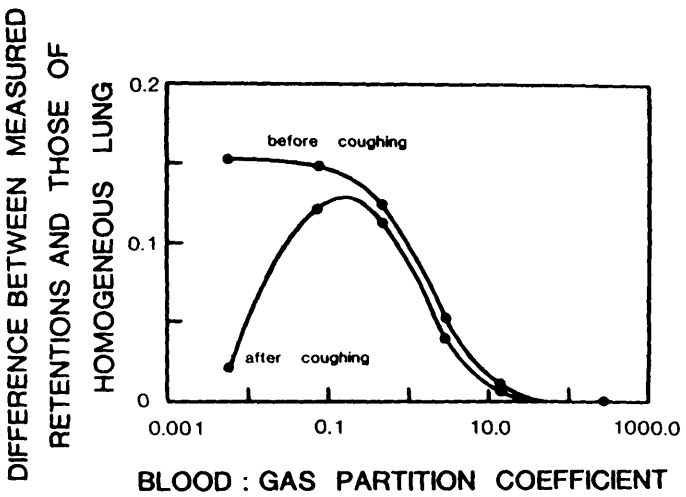


**Figure 4** Difference between measured inert gas retentions and those expected in a homogeneous lung having the same total ventilation and blood flow. Results obtained both before and after coughing are shown. Notice a major difference, particularly for the least soluble gas, SF6 (partition coefficient 0.005).

globin for oxygen, increasing $P_{50}$ by about 1.5 mmHg/°C, shifting the ODC curve to the right, reducing for a given $Po_2$ the capacitance of the blood for $O_2$. Other than in severe arterial and mixed venous hypoxemia, which are frequent during ARF, this shift reduces arterial hypoxemia, as $Pao_2$ for a given $\dot{V}/\dot{Q}$ is a function of the capacitance of the blood for oxygen (Fig. 1). Furthermore, this shift enhances the $O_2$ diffusion to tissues as for a given $So_2$, $Po_2$ is higher when the ODC curve is shifted to the right. However, in deep hypoxemia, the $O_2$ concentration in the blood for a given $Pao_2$ is lower than when the curve is in the normal position, therefore a limitation in the $O_2$ concentration in this condition could appear.

Following the Arrhenius or Vant'Hoff $Q_{10}$ law, an increase in central temperature should increase the metabolism slightly and $O_2$ consumption about 10–12% per °C. Dubois reported a 13% per °C increase (62), which in cases of ARF necessitates using compensatory mechanisms to avoid a decrease in $P\bar{v}o_2$. More important, perhaps, is the release of pyrogens—either exogenous, like the very active endotoxins produced by gram-negative bacteria, or endogenous, released by leukocytes. These pyrogens are responsible at the onset of fever for episodes of shivering during which $O_2$ consumption can be two to five times normal. It might be that some patients with severe COPD reach their maximal oxygen consumption during these bursts of $O_2$ demand, which could be potential causes of ARF, as they need rapid compensatory mechanisms to avoid blood and tissue hypoxia. Further-

more, the injection of the *E. coli* endotoxin (1 mg/kg lipopolysaccharide) to unanesthetized sheep ends hypoxic pulmonary vasoconstriction and therefore increases the heterogeneity of the distribution of perfusion (63). The staphylococcal α-toxin induces a marked pulmonary vasoconstriction with severe $\dot{V}/\dot{Q}$ mismatch and interstitial edema. These effects are suppressed by thromboxane inhibition (64).

### B. Thrombosis and Pulmonary Embolism

The effect of thrombosis or pulmonary embolism (PE) on gas exchange in patients with COPD has not been described in detail as it has been in patients without COPD. This is probably due both to the difficulties of the diagnosis of PE in COPD patients (65) and to the lack of knowledge of the gas-exchange status of the patient before a PE episode. Nevertheless, in some cases PE has been suspected upon rapid alterations in blood gases—a decrease in $Pa_{CO_2}$ suggesting an increase in ventilation and a decrease in $Pa_{O_2}$ suggesting an increase in $\dot{Q}$ heterogeneity and/or a fall in $P\bar{v}_{O_2}$. An increase in $(a\text{-}A)D_{CO_2}$, provided that a previous measure has been made, can be related to more heterogeneity in $\dot{V}$ distribution, i.e., to more "wasted" ventilation. This difference may be used to estimate the percentage (q%) of ventilation in poorly perfused or unperfused regions of the lung. Using the equation of Severinghaus and Stupfel (66):

$$q = 100 \times \frac{(Pa_{CO_2} - P_{A_{CO_2}})}{Pa_{CO_2}}$$

or to take into account the effect of the rebreathing of $CO_2$ in the unperfused spaces

$$q = 100 \times \frac{(Pa_{CO_2} - P_{A_{CO_2}})}{[Pa_{CO_2} - P_{A_{CO_2}} + P_{E_{CO_2}}]}$$

where $P_{A_{CO_2}}$ and $P_{E_{CO_2}}$ are mean alveolar and mean expired $CO_2$ partial pressures, respectively. The correlation between this estimation and the percentage of ventilation in $\dot{V}/\dot{Q}$ compartment above a figure of 10, using the MIGT, is fair in both pulmonary embolism and COPD (Fig. 5). The fall in $Pa_{O_2}$ and the increase in $(A\text{-}a)D_{O_2}$ could be due to a true shunt, a greater heterogeneity in $\dot{Q}$ distribution, or a decrease in $P\bar{v}_{O_2}$. Because $Pa_{O_2}$ increases less in COPD patients with PE ventilated with pure $O_2$ than in COPD patients without PE, Chopin et al. suggested that a true shunt can be, at least in part, the cause of the fall in $Pa_{O_2}$ (67). The increase in the right ventricle telediastolic and atrial pressures could even reopen the foramen ovale (6). However, the diagnosis of a true shunt with the $O_2$ method is questionable in patients with a great $\dot{V}/\dot{Q}$ mismatch. Mean pulmonary arterial pressure in a patient with PE and COPD is no different from a COPD patient without PE, as the cardiac index is lower in the patient with PE (67,68). Manier

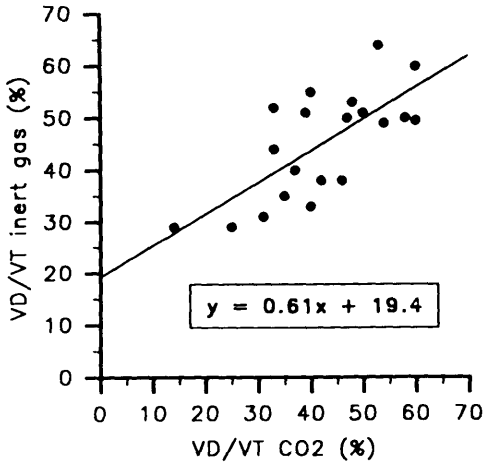


**Figure 5** Correlation between the inert gas dead space (derived form the multiple inert gas technique), including the percentage ventilation in all $\dot{V}/\dot{Q}$ units above a figure of 10 and the $Co_2$ parallel dead space according to the equation of Suwa and Bendixen (67), in 20 patients with COPD recovering from ARF. Although both methods of calculation of these dead spaces rely on different assumptions which could explain the scatter of the points the correlation between the two estimates of the dead spaces is fair. The y value for x = 0, about 20%, is close to the estimated series dead space which is included in the inert gas dead space value. It is worthy to note the high percentage of "wasted" ventilation reached by some COPD patients (mean 42%) (4).

and Castaing (69) evaluated the influence of cardiac output on gas exchange in acute PE. They found that $P\bar{v}O_2$ was directly related to the cardiac index and negatively related to the mean $\dot{V}/\dot{Q}$ of blood flow distribution, both of which are factors of arterial hypoxemia. Furthermore, the pattern of $\dot{V}/\dot{Q}$ distributions was found to depend on cardiac output. However, no specific measurement of $\dot{V}/\dot{Q}$ distribution using the inert gas method seems to have been made in COPD patients with PE. It could be speculated that patients with an initial H pattern would increase the amount of $\dot{V}$ in high $\dot{V}/\dot{Q}$ units. However, the redistribution of blood flow in the remaining parenchyma would increase blood flow in low $\dot{V}/\dot{Q}$ units, suggesting that these patients could switch from an H to an HL pattern. L patients would improve their $\dot{Q}$ distribution if thrombosis or PE occurs in low $\dot{V}/\dot{Q}$ units. However, they would tend to develop an H pattern if thrombosis or PE occurs in normal $\dot{V}/\dot{Q}$ units. Therefore, a trend to a mixed pattern (HL) should be the final status of patients initially of either H or L patterns after diffuse thrombosis or PE.

Thrombosis in ARF patients with COPD is well documented in pathological

findings (10). The only way to diagnose thrombosis is to label the patient platelets with a radioactive tracer and, after reinjection of the platelets, to perform a lung scintigraphy. Entrapment of platelets has been documented during ARF (70), and hypoxemia has been suggested to activate platelets (71), however, no specific study of gas exchange in patients with thrombosis seems to have been performed.

### C. Hypoventilation

Rapid, shallow breathing is one clinical feature of patients with ARF. This pattern of breathing may result from different causes, among which respiratory muscle fatigue is likely to play a determinant role. This may alter gas exchange in two ways: decreasing alveolar ventilation and increasing the heterogeneity of the distribution of $\dot{V}$. A decrease in overall alveolar ventilation is often associated with this breathing pattern, as $\dot{V}A = (VT - VDS) \times f$, where VDS stands for series dead space. Keeping $\dot{V}A$ constant requires a balance between the decrease in VT and the increase in f, which may be difficult to accomplish as f in the basal state of COPD is often high. If $\dot{V}A$ decreases, mean alveolar $PCO_2$, $PA_{CO_2}$, increases. The relationship between $\dot{V}A$ and $PA_{CO_2}$ for a given $CO_2$ output, $\dot{V}CO_2$, is curvilinear:

$$PA_{CO_2} = K \times \dot{V}CO_2/\dot{V}A$$

where K is a constant. The slope of this curve, i.e., the $\Delta PA_{CO_2}$ induced by $\Delta VA$, is inversely related to the square of $\dot{V}A$:

$$\Delta PA_{CO_2}/\Delta\dot{V}A = K \times \dot{V}CO_2/\dot{V}A^2$$

This change in slope with $\dot{V}A$ is worth considering, as it is about 2 and 25 mmHg L/min for $\dot{V}A$ of 10 and 3 L/min respectively, $\dot{V}CO_2$ being 270 ml/min. Therefore, a very small decrease in alveolar ventilation would increase $PA_{CO_2}$ by several mmHg in patients having a low alveolar ventilation.

Stradling (72) analyzed the data of Aubier et al. (59) in which pure $O_2$ was given to patients with ARF and COPD. The data showed a rise in $PaCO_2$ from 65 to 88 mmHg, a slight fall in VT from 341 to 323 ml and in f from 32 to 31; instrument dead space was 75 ml. Stradling, by assuming a series dead space of 175 ml, found a fall of 22% in alveolar ventilation, from 2.9 to 2.26 L/min, which for the author would just fit the arterial, not the alveolar, $PCO_2$ alterations. However, it seems surprising that such patients had no alveolar-to-arterial $PCO_2$ differences, i.e., no $\dot{V}/\dot{Q}$ mismatch. The set value of 175 ml for series dead space is probably too high; a value of 140 ml (53) would seem more accurate. Taking this figure into account leads to $\dot{V}A$ values of 4.0 and 3.35 L/min and to $PaCO_2$ values of 59 and 70 mmHg in air and $O_2$ conditions, respectively. These calculations show that very small alterations in the figures are followed by great alterations in derived data and that the conclusion drawn from such data depends on slight alterations in hypotheses. The equation

$$P_{A_{CO_2}} = \dot{V}CO_2 \times K/(VE - VDphys) \times f$$

in which $PaCO_2$ and VDphys replace $P_{A_{CO_2}}$ and VDS from the alveolar equation, should be considered more carefully than the alveolar equation, as VDphys, for a given heterogeneity of the distribution of $\dot{V}/\dot{Q}$, is a function of the overall ventilation (49).

### D. Nutrition

Muscle weakness due to malnutrition is considered to be a potential cause of ARF in COPD patients (73). High-carbohydrate diets have been suspected to favor respiratory failure by increasing $CO_2$ load (74). Furthermore, intravenous fat emulsion can alter $\dot{V}/\dot{Q}$ distribution (75). Shifting the metabolism from pure fat oxidative consumption to pure carbohydrate consumption should increase $\dot{V}CO_2$, given the same energy production and the same oxygen consumption, by 30%. This effect has been reported by many groups. For example, Saltzmann and Salzano (76) observed a 43% increase in $\dot{V}CO_2$, 47% in $\dot{V}A$, 13% in $\dot{V}O_2$, and 25% in VT in five resting young men after the ingestion of 920 kcal following 16 hours of fasting, whereas $P_{A_{CO_2}}$ and $(A\text{-}a)DO_2$ were unaffected as $PaO_2$ increased by 9 mmHg. However, this abrupt shift from fat to carbohydrate metabolism should occur only if the intake exactly fits the needs. If caloric intake is not sufficient, lipolysis and perhaps proteolysis will occur, for if intake is greater than needed for the basal metabolism, the substrates will be stored in part as fat via lipogenesis or in debilitated people possibly as proteins. The production of $CO_2$ through these different pathways is very different, as the value of R is 0.8 for lipolysis and 8 for lipogenesis. According to Talpers et al. (77), an increase in $CO_2$ production is due to an increase in total energy intake and not to a specific carbohydrate intake. Isocaloric intakes with various proportions of carbohydrate did not alter $CO_2$ production (about 205 ml/min in mechanically ventilated patients), but a progressively increasing caloric intake did increase $\dot{V}CO_2$ production. These findings are of interest in the efforts to avoid additional $CO_2$ load in COPD patients with ARF, although their basic explanation is yet lacking. The effect of intravenous fat emulsion on gas exchange in patients with respiratory failure has been studied by Hwang et al. (75) in several groups of patients, one of them including 12 patients with ARF. In COPD patients, there was no change in the ratio of $PaO_2$ to $FIO_2$ during 12 hours after a 4-hour infusion of 500 ml of fat emulsion (10% Lyposin I), whereas the group of patients with ARDS worsened. A possible explanation for this effect is the release of prostaglandins after fat infusion, as the substrates used are in great part made of polyunsaturated fatty acids, precursors of prostaglandins, which may be either vasodilating ($PGE_1$) or vasoconstrictive ($PGF_2\alpha$) (78). Lungs with injured pulmonary capillaries would be more sensitive to fat emulsion perfusion.

It is worth noting that the metabolic needs of patients refer to standard

resting energy expenditure (REE), which is difficult to standardize in patients having very different physiological (age, weight, height, central temperature, level of respiratory load) or medical (ventilatory support, medication, mode of feeding) status. REE values are usually based on the Harris and Benedict equation (79), which has been believed to be loosely applicable to critically ill patients (80). It is therefore difficult to estimate the optimal need of any one patient.

## III. Therapies

Apart from mechanical ventilation, treatment of decompensated COPD includes correction of metabolic abnormalities, antibiotics, controlled low-flow oxygen, low-dose heparin, physiotherapy, bronchodilators, corticosteroids, nutritional support, and sometimes respiratory stimulants (81). All of these interventions are assumed to result, directly or indirectly, in an improvement in pulmonary gas exchange. However, in this respect, only supplemental oxygen, bronchodilators, the peripheral chemoreceptor stimulant almitrine, and drugs used as pulmonary vasodilators have been specifically investigated.

### A. Oxygen

Oxygen is used either as a therapy or as a test to estimate the shunt fraction.

#### *Pure $O_2$ Breathing*

One hundred percent $O_2$ is often used to differentiate hypoxemia due to true right-to-left shunt from $\dot{V}/\dot{Q}$ heterogeneity. This is not accurate for two reasons: (1) some lung units may have a very slow rate of $N_2$ washout, needing more than the usual 30 minutes of pure $O_2$ to be cleared from $N_2$, and (2) the distribution of $\dot{V}/\dot{Q}$ may change when $O_2$ is given. To be effective in 30 minutes, a washout with pure $O_2$ would need lung units with a time constant below 10 minutes; as much as 3 time constants are sufficient to clear the lung from nitrogen. This figure is clearly less than those observed by many authors. Furthermore, the fraction of the alveolar volume with a given time constant is inversely correlated to ventilation, i.e., there is more lung volume involved in poorly ventilated than in well-ventilated regions (82).

#### *Alteration in $\dot{V}/\dot{Q}$ Distribution with Pure $O_2$ Breathing*

The alteration in $\dot{V}/\dot{Q}$ distribution due to $O_2$ breathing can be due to several factors: (1) the collapse of some alveoli, (2) the alteration in the distribution of perfusion due to the increase in $Pa_{O_2}$ and $P\bar{v}_{O_2}$ releasing hypoxic vasoconstriction, (3) the change in the mechanical properties of opened alveoli surrounding collapsed alveoli, and (4) the change in the pattern of breathing.

As the $O_2$ uptake of the blood could be greater than the $O_2$ supplied by the ventilation, low $\dot{V}/\dot{Q}$ units are liable to collapse. $\dot{V}/\dot{Q}$ values lower than 0.08 are theoretically critical when 100% $O_2$ is breathed for about 1 hour (83,84). Moreover, at the onset of $O_2$ inhalation, the perfusion in a low $\dot{V}/\dot{Q}$ zone could rise as a consequence of the release of hypoxic vasoconstriction, leading to an even lower $\dot{V}/\dot{Q}$ value. Several clinical studies confirm the alterations in $\dot{V}/\dot{Q}$ distribution as well as the increase in shunt fraction (4,85). By contrast, mechanically ventilated patients with ARDS but without COPD did not increase their shunt fraction while breathing 100% $O_2$ (86) as did patients with severe bacterial pneumonia (87,88). In ARDS patients the difference is likely to be due to the presence of a true shunt, the remaining parenchyma being close to normal $\dot{V}/\dot{Q}$, as patients with COPD have few shunts, the hypoxemia being due to perfusion in low $\dot{V}/\dot{Q}$ areas. However, in bacterial pneumonia this difference is not observed, and pure $O_2$ breathing does not increase the shunt fraction. There is no clear explanation for this discrepancy. It could be that the change in lung structure in COPD patients alters the mechanical properties of the alveoli and bronchi, which become more liable to collapse when $O_2$ is breathed.

It has been suggested that a lower $F_{IO_2}$, e.g., between 0.4 and 0.6, could be useful in estimating the right-to-left shunt fraction and avoiding the deleterious effects of pure $O_2$. However, in this situation the $(A\text{-}a)D_{O_2}$ difference in a heterogeneous lung without shunt is strongly dependent on the heterogeneity of $\dot{V}/\dot{Q}$ (49). Therefore, no clear interpretation of the $(A\text{-}a)D_{O_2}$ can be made when heterogeneity of both $\dot{V}/\dot{Q}$ and shunt are present.

According to Castaing et al. (89), hypoxic vasoconstriction could be active in lung units with a $P_{AO_2}$ of 50 mmHg or less during air breathing. In ARF patients with severe hypoxemia, this threshold is likely to be reached in a major part of the lung. In such conditions the expected regional increases in blood flow due to the release of vasoconstriction would require an increase in cardiac blood flow during $O_2$ breathing to be significant. Such an increase has not been observed (59,67), thus the release of the hypoxic vasoconstriction in low $\dot{V}/\dot{Q}$ units should be followed by a decrease in perfusion in normal or high $\dot{V}/\dot{Q}$ units, which would raise their $\dot{V}/\dot{Q}$ ratios. Therefore the effect of the redistribution of blood flow due to the release of hypoxic vasoconstriction should be small in ARF patients.

As some alveoli are likely to collapse during $O_2$ breathing, neighboring alveoli should be distended and should tend to decrease their ventilation. This interdependency within the parenchyma is a well-recognized fact, although the specific effect of $O_2$ lacks experimental evidence. Mead et al. (90) suggest that the alveolar network opposes nonuniform changes in size of one region compared to another. However, a heterogeneous distribution of stresses within the parenchyma, as in patients with COPD, should be more sensitive to slight disequilibrium, such as the trend of some alveoli to collapse.

The breathing pattern can be altered by inhalation of $O_2$, however, after a few minutes of hyperoxia the decrease in $V_E$ is small and not significant either in patients with ARF (59) or in COPD patients without ARF (50). In the former case $V_T$ was decreased, while in the latter f was decreased. These slight and inconstant changes in the pattern of breathing seem meaningless as specific factors of $\dot{V}/\dot{Q}$ alterations, unless $\dot{V}/\dot{Q}$ distribution is sensitive to small changes in the pattern of breathing. It might be that patients with high regional airway closure capacity worsen their $\dot{V}/\dot{Q}$ distribution when $V_T$ is decreased, but Read and Lee were unable to find a significant change in $V_D$ (physiological)/$V_T$ ratio in COPD patients having $V_T$ spontaneous fluctuations of 40 ml or more (91).

### *Hypercapnia During $O_2$ Breathing*

The determinants of hypercapnia during $O_2$ breathing are the subject of controversy. According to Aubier et al. (59), hypercapnia is mainly due to $\dot{V}/\dot{Q}$ mismatch and the Haldane effect. Stradling (72), using data from Aubier et al., attributes the hypercapnia mainly to hypoventilation and to the Haldane effect. Sasoon et al. (50) by analyzing carefully the different causes of hypercapnia in stable COPD patients attributed the main cause to $\dot{V}/\dot{Q}$ mismatch. Guenard et al. (85) showed with radioactive-labeled nitrogen scintigraphies a fall in V in some lung regions having initial $\dot{V}/\dot{Q}$ below 0.7 while breathing air. Therefore, several arguments, either theoretical or experimental, support the concept of a deleterious effect of pure $O_2$ on $\dot{V}/\dot{Q}$ distribution.

Christiansen et al. (92) described the shift of the $CO_2$ concentration-pressure relationship under the effect of various saturations of hemoglobin with $O_2$. For a given $P_{CO_2}$, the $CO_2$ concentration in the blood decreases with $S_{O_2}$, therefore when $Sa_{O_2}$ and $S\bar{v}_{O_2}$ are raised by inhaling $O_2$, some $CO_2$ is released from the red cells. The difference in $CO_2$ concentrations between reduced and oxygenated fresh blood is about 5–6 ml% in the range of patients $Pa_{CO_2}$. Therefore, the shift from reduced hemoglobin to the oxygenated form releases 250–300 ml $CO_2$ in 5 liters of blood, that is, the equivalent of one minute of the $CO_2$ production of a patient at rest. In patients with worst-case ARF, an increase of 50% in arterial and venous $O_2$ saturation could occur, i.e., 125–150 ml $CO_2$ would be released. The shift from the reduced to the oxygenated state at constant $CO_2$ concentration would increase $Pa_{CO_2}$ by about 8 mmHg (93). The amount of $CO_2$ released, and the resulting hypercapnia, would be washed out with a time constant $V/\dot{V}_A$, where V and $\dot{V}_A$ are lung volume and alveolar ventilation, respectively. Therefore, most of the $CO_2$ overload should be washed out in a few minutes.

Another consequence of the Haldane effect resides in the heterogeneous distribution of $\dot{V}/\dot{Q}$. The inhalation of $O_2$ raises $Sa_{O_2}$ more in low $\dot{V}/\dot{Q}$ units than in high $\dot{V}/\dot{Q}$ units, the latter always having high $Sa_{O_2}$. Thus, more $CO_2$ will be released in low $\dot{V}/\dot{Q}$ units and $Pa_{CO_2}$ would increase. The increase in $Pa_{CO_2}$ would

depend on numerous factors, but in all cases should be very small and hardly detectable. Stradling (72), in a severe ARF example, gives a 3 mmHg figure.

### *Low $O_2$-Enriched Air*

Supplemental oxygen, the only treatment of established clinical efficacy in COPD (94,95), is generally believed to unload the right ventricle and to increase oxygen delivery to the tissues (96). Theoretically, oxygen should deteriorate pulmonary gas exchange by a release of hypoxic vasoconstriction. This mechanism was identified by Lee and Read (97), who in 1967 reported an increase in physiological dead space in patients with COPD breathing supplemental oxygen. However, alternative explanations include an oxygen-induced decrease in cardiac output (98) or an altered distribution of ventilation because of decrease in bronchomotor tone (99) and/or a change in the pattern of breathing (59)—not to mention the effect of oxygen-induced increase in arterial $P_{CO_2}$.

No study of the distribution of $\dot{V}$ and $\dot{Q}$ during ARF in COPD seems to have been performed with $O_2$-enriched air. However, when Castaing et al. (89) did $\dot{V}/\dot{Q}$ measurements with the inert gas method in severe COPD patients breathing either air or 26% $O_2$, $P_{aO_2}$ rose from 55 to 75 mmHg. This rise in arterial oxygenation was impeded by a slight increase in $\dot{V}/\dot{Q}$ mismatch due to a 3% increase in perfusion in $\dot{V}/\dot{Q}$ compartments having a $P_{aO_2}$ of 50 mmHg or less during air breathing. An increase in $\dot{V}/\dot{Q}$ mismatching was also found by Eiser et al. (100) using a scintigraphic technique in 16 patients breathing 30% $O_2$. Gea et al. (88) found an increase in the heterogeneity of the distribution of perfusion in patients either breathing spontaneously or mechanically ventilated when they were switched from their clinically needed $F_{IO_2}$ mixture to 100% $O_2$. However, the effect of a slight increase in $F_{IO_2}$ was not studied.

For Melot (101), the effect of an increase in $F_{IO_2}$ on hypoxic vasoconstriction remains controversial, as he failed to find an effect on gas exchange in 20 patients. In this work the multiple inert gas technique was used to investigate the effect of 28 or 40% supplemental oxygen on the distribution of $\dot{V}/\dot{Q}$ in two different groups of, respectively, 9 and 11 patients stabilized after admission for decompensated COPD. Both groups of patients were hypoxemic and hypercapnic and presented with a moderate pulmonary hypertension. In both groups of patients, oxygen markedly increased blood oxygenation and slightly increased arterial $P_{CO_2}$ without change in pulmonary hemodynamics or in ventilation. Interestingly, 40% oxygen breathing was associated with a decrease in airway resistance (Table 1). Supplemental oxygen did not affect the inert gas retention–excretion difference, indicating no effect on pulmonary gas exchange (Fig. 6). These results can be explained either by an oxygen-induced increase in both perfusion and ventilation to low $\dot{V}/\dot{Q}$ units or by the fact that neither hypoxic

**Table 1** Effects of 40% $F_IO_2$ on Blood Gases, Respiratory Parameters, and Hemodynamics in Patients with ARF on COPD

| | $F_{IO_2}$0.21 | $F_{IO_2}$0.40 | *p* |
|---|---|---|---|
| $Pa_{O_2}$, mmHg | 53 ± 3 | 133 ± 8 | <0.001 |
| $Pa_{CO_2}$, mmHg | 49 ± 2 | 53 ± 3 | <0.01 |
| $P\bar{v}_{O_2}$, mmHg | 33 ± 1 | 44 ± 1 | <0.001 |
| Raw, $cmH_2O/l \cdot s$ | 133 ± 1.4 | 108 ± 1.6 | <0.05 |
| $\dot{V}_E$, l/min | 9.5 ± 1.0 | 9.8 ± 1.1 | NS |
| $\dot{Q}$, $l/min.m^2$ | 2.8 ± 0.1 | 2.7 ± 0.3 | NS |
| Ppa, mmHg | 26 ± 3 | 27 ± 3 | NS |
| Ppo, mmHg | 3 ± 1 | 3 ± 1 | NS |
| PVR, $dyne \cdot s \cdot cm^{-5} \cdot m^2$ | 685 ± 108 | 711 ± 121 | NS |

*Source*: Ref. 101.

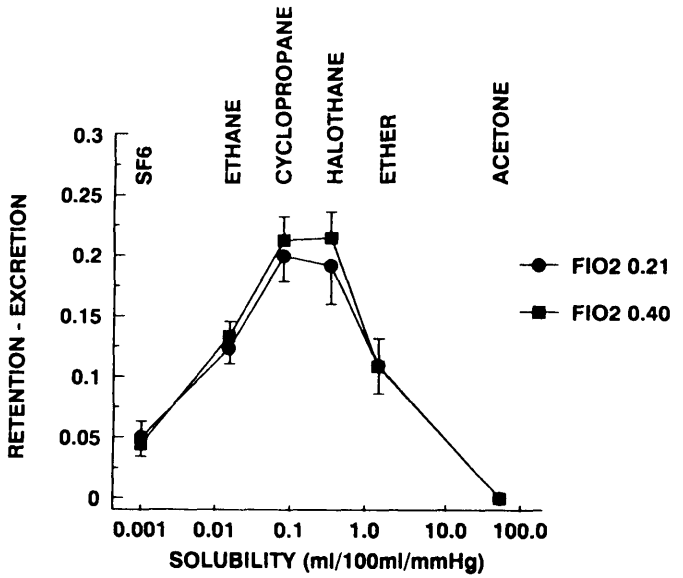


**Figure 6** Mean ± SEM (vertical bars) retention-excretion differences versus solubility for 6 inert gases, in normoxia ($F_{IO_2}$ 0.21) (circles) and in hyperoxia ($F_{IO_2}$ 0.40) (squares), in 12 patients with COPD. Supplemental oxygen had no effect. Data for $F_{IO_2}$ = 0.28 are not shown, but are close to those illustrated in this figure (After Melot) (101).

vasoconstriction nor hypoxic bronchoconstriction contribute to gas exchange in decompensated COPD.

These conflicting results suggest that hypoxic vasoconstriction is released by an $F_{IO_2}$ increase in some, but not all, patients, and that its effects on gas exchange, if any, are limited. Whatever the effect on gas exchange, all authors agree on the lack of hemodynamic effect of an $F_{IO_2}$ increase (98,99,102,103). This finding reinforces the conclusion of a slight effect of an increase in $F_{IO_2}$ on hypoxic vasoconstriction. The use of inhaled NO as a selective vasodilator of high $\dot{V}/\dot{Q}$ units by shifting the blood from low $\dot{V}/\dot{Q}$ to high $\dot{V}/\dot{Q}$ compartments should reduce the mismatch induced by $O_2$ breathing.

It is worth noting that ARF patients not altered by adult respiratory distress syndrome (ARDS) but with a weak cardiac function may have a dependency of oxygen uptake upon oxygen delivery like ARDS patients. Among the patients of Dorinsky et al. (104) having such a dependency, one patient had COPD and PE, while the others had either myocardial infarction, pneumonia, cardiomyopathy, or congestive heart failure. Their cardiac index was $2.6 \pm 0.3$ L/(min·m$^2$), a figure close to that reported in the literature for ARF patients with COPD. For example, Chopin et al. (67) reported cardiac indexes of $2.4 \pm 1.3$ and $2.8 \pm 1.15$ in patients with and without PE.

### B. Mechanical Ventilation and Gas Exchange

Mechanical ventilation (MV) in patients with COPD is commonly employed as a life-saving therapeutic modality. It affords the patient with ventilatory failure the opportunity to rest the respiratory muscles while maintaining pH and gas-exchange homeostasis. This section outlines key considerations in the interaction of the mechanical ventilator with gas exchange in COPD patients during ventilatory support and during the process of machine withdrawal.

#### *Pathological Consequences of MV on Gas Exchange*

The positive pressure difference between the mouth and distal airways that is generated during mechanical ventilation both increases mean intrathoracic pressure and decreases transmural pressure of IT vessels. In COPD patients, with increased airway resistance, less airway pressure is transmitted. Nevertheless, the development of a potential intrinsic positive end-expiratory pressure (PEEP) due to airflow limitation can magnify this phenomenon, especially if large tidal volumes are used to fully compensate hypercapnia and return the $P_{ACO_2}$ to the normal level. This decrease in IT vessel transmural pressure reduces both right ventricular filling pressures and left ventricle afterload (105), leading to a decrease in the cardiac output ($\dot{Q}_c$). This deleterious cardiovascular effect and its consequences on $\dot{V}/\dot{Q}$ ratio distribution have never been extensively studied. Nevertheless, the work of Torres et al. (106) shows that this change in cardiac output in

COPD patients during a weaning period without right or left heart failure leads to better $\dot{V}/\dot{Q}$ relationships during mechanical ventilation than during spontaneous breathing. The combined effects of the increase in the efficiency of minute ventilation (lower respiratory frequency and higher $\dot{V}_T$ during MV) and the concomitant decrease in $\dot{Q}_c$ shift to the right (towards high $\dot{V}/\dot{Q}$ ratios) the distributions of $\dot{V}$ and $\dot{Q}$ as a function of $\dot{V}/\dot{Q}$. The percentage of blood flow through low $\dot{V}/\dot{Q}$ areas ($\dot{V}/\dot{Q} < 0.1$) is 10% lower during MV than during spontaneous breathing. At maintenance $F_{IO_2}$, $Pa_{O_2}$ is not significantly different in both ventilatory conditions, although $P\bar{v}_{O_2}$ is lower during MV. It can be concluded that the decrease in $P\bar{v}_{O_2}$ is compensated for by the reduction in $\dot{V}/\dot{Q}$ inequalities, provided that $\dot{V}_{O_2}$ is identical in both breathing conditions.

An alveolar filling process such as pneumonia or a fall in functional residual capacity below the closing capacity increases the percentage of intrapulmonary shunt or venous admixture during acute respiratory failure in these patients. In the above-mentioned study (106), the mean value of inert gas shunt in eight COPD patients requiring MV for ARF was approximately 20% of cardiac output, whereas it is always lower than 5% in stable patients. The intrinsic PEEP (PEEPi) due to expiratory flow limitation should reduce the shunt fraction. The application of external PEEP can reduce the inspiratory load due to PEEPi without further hyperinflation or any increase in intrathoracic pressure (107). The effects on hemodynamic and gas exchange were specified by Ranieri et al. (108) in nine mechanically ventilated patients with COPD. They showed that PEEP levels exceeding 85% of PEEPi caused hyperinflation and altered hemodynamics and gas exchange even if $Pa_{O_2}$ is increased. These data provide a physiological rationale for the use of low levels of PEEP in COPD patients during MV.

Several other ventilator modes have been suggested to prevent undesirable barotraumatic effects or complications. The omission of the end-expiratory pause has a detrimental effect on gas exchange—the shorter the time of insufflation, the worse the effect (109). An inverse ventilation ratio, rather reserved for patients with diffuse lung disease and severe hypoxemia, would be dangerous in the presence of airflow limitation generating high levels of intrinsic PEEP.

### *Gas Exchange During the Weaning Period*

Gradual withdrawal of mechanical ventilation in COPD, with or without volume or pressure partial support adjusted to patient requirements, takes two to three times longer than the mean duration of the weaning period in other patients undergoing MV (110,111). As a general rule, patients with COPD must not be reexposed abruptly to spontaneous breathing as, owing to the obstruction, the ventilatory increase in workload would be too high and the respiratory muscles too weak. In addition, in COPD patients, the discontinuation of MV increases $\dot{V}/\dot{Q}$ inequalities at maintenance $F_{IO_2}$ without any change in $Pa_{O_2}$ (see above). These

results seem to be characteristic of COPD patients, as other studies (17,112,113) found better $\dot{V}/\dot{Q}$ relationships when non-COPD patients were breathing spontaneously. This impairment in $\dot{V}/\dot{Q}$ distribution, not detected by conventional arterial blood gas measurements alone, can be explained by considerable changes in the breathing pattern as well as by changes in cardiovascular function.

### C. Drugs

Studies on the effects of drugs on gas exchange in decompensated COPD include measurements of ventilation, airway resistance, pleural pressure, lung volumes, pulmonary hemodynamics, arterial and mixed venous blood gases, and a functional distribution of $\dot{V}/\dot{Q}$ using the multiple inert gas elimination technique. This approach allows a quantification of the pulmonary and extrapulmonary contributions to the composition of arterial blood gases, but cannot sort out the separate effects of changes in the distributions of ventilation and perfusion, respectively, on the recovered arterial blood gases, distributions of $\dot{V}/\dot{Q}$, or inert gas retention or excretion. The mathematical lung model used by the multiple inert gas elimination technique constrains all alveoli to have one of 50 $\dot{V}/\dot{Q}$ values evenly spaced on a logarithmic scale where ventilation and perfusion distributions are linked together. As illustrated in Figure 7, for a high $\dot{V}/\dot{Q}$ ratio, the slope of $\dot{V}/\dot{Q}$ isopleths is steep, and the same change in $\dot{V}/\dot{Q}$ can arise either from subtle, hardly measurable, changes in blood flow, or from huge changes in ventilation (114). Conversely, for a low $\dot{V}/\dot{Q}$ ratio, the slope of $\dot{V}/\dot{Q}$ isopleths is shallow, and the same change in $\dot{V}/\dot{Q}$ can arise from an easily measurable drop in perfusion or a subtle, unmeasurable increase in ventilation (115). Since different combinations of ventilation and perfusion changes may account for a resulting $\dot{V}/\dot{Q}$ distribution, conclusions drawn from the MIGT data remain speculative until confirmed by separate determinations using high-resolution isotopic methods, which provide measurement of ventilation and perfusion per unit lung volume. This is particularly important for interventions susceptible to affect both pulmonary vasomotor and bronchomotor tone, as in the case of some drugs.

#### *Bronchodilators*

Theophylline was first reported to deteriorate arterial oxygenation in patients with COPD by Hamalgui and Coates in 1959 (116). This effect was confirmed by others and tentatively explained by an inhibition of hypoxic pulmonary vasoconstriction. However, theophylline has been reported to inhibit hypoxic vasoconstriction in some experimental animal studies (117) but not in others (118). It may be that theophylline inhibits the hypoxic pressor response only at plasma levels higher than 20 μg/ml, considered to be supra-therapeutic (119). Barbera et al. (120) investigated the effects of aminophylline at clinically relevant doses and 100% oxygen, alone or in combination, on the distribution of $\dot{V}/\dot{Q}$ determined

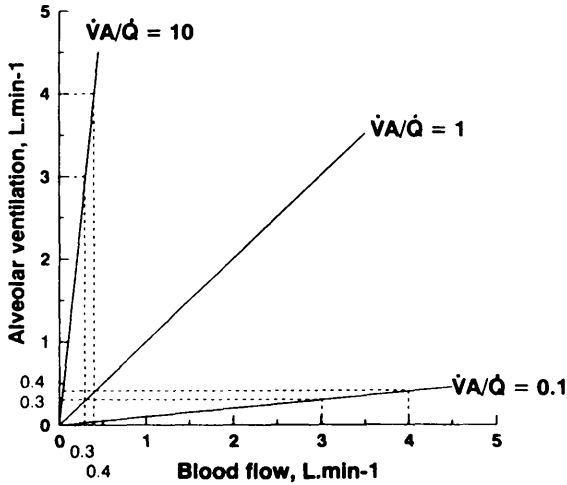


**Figure 7** Alveolar ventilation ($\dot{V}_A$) versus blood flow ($\dot{Q}$) with $\dot{V}/\dot{Q}$ isopleths ($\dot{V}/\dot{Q}$ = 0.1, 1 and 10). $\dot{Q}$ and $\dot{V}_A$ are both arbitrarily fixed a 4 l/min. In a low $\dot{V}/\dot{Q}$ area ($\dot{V}/\dot{Q}$ = 0.1), the slope is flat and an easily measured change in $\dot{Q}$ from 4 to 3 l/min, a 25% change, correspond to a hardly detectable decrease in $\dot{V}_A$, from 0.4 to 0.3 l/min, a 2.5% change. Conversely, in a high $\dot{V}/\dot{A}$ area ($\dot{V}/\dot{Q}$ = 10), the slope is steep and an easily measurable decrease in $\dot{V}_A$ from 4 to 3 l/min (25%) corresponds to a hardly measurable decrease in $\dot{Q}$, from 0.4 to 0.3 l/min (2.5%) (After Castaing et al.) (115).

by MIGT in patients during the recovery of an exacerbation of COPD. Aminophylline alone had no effect, but pure oxygen induced a modest increase in perfusion to lung units with lower than normal $\dot{V}/\dot{Q}$. This effect was slightly enhanced when aminophylline was given in combination with oxygen. The authors interpreted these results as being the consequence of pulmonary vascular effects of $O_2$ and of theophylline, but they did not consider the possibility of a change in the distribution of ventilation related to the bronchodilating effects of both interventions.

$Beta_2$-adrenergic agonists have been reported to either decrease (121) or not affect (122) arterial oxygenation in stable COPD. Ringsted et al. (123) investigated the effects of intravenous terbutaline on $\dot{V}/\dot{Q}$ distributions determined with MIGT in 11 patients. They found an increase in the retention-excretion difference for the inert gases, which was maximal for the lung units with lower than normal $\dot{V}/\dot{Q}$. This was tentatively explained by a release of hypoxic pulmonary vasoconstriction. However, terbutaline increased both ventilation and cardiac output and probably affected both bronchomotor and vasomotor tone with therefore unpredictable effects on the respective topographic distributions of ventilation and

perfusion. In the same study, it occurred that terbutaline-induced deterioration in $\dot{V}/\dot{Q}$ matching was minimal in the most hypoxemic patients. Ringsted et al. (123) therefore speculated that the most advanced stages of COPD might be associated with a loss of the hypoxic pressor response. However, Weitzenblum et al. (124) reported that the magnitude of the whole lung pressor response to hypoxia in patients with stable COPD was not related to arterial blood gases, lung mechanic alterations, or severity of pulmonary hypertension.

### *Vasodilators*

Nifedipine has been shown to inhibit hypoxic vasoconstriction in experimental animals (125) and in normal humans (126,127) and has been repeatedly experimented with as a treatment of pulmonary hypertension secondary to COPD (96). Melot et al. (128) investigated the effects of a reduction in pulmonary vascular resistance by this calcium channel blocker on the distribution of $\dot{V}/\dot{Q}$ determined by the MIGT in six patients with decompensated but stabilized COPD. Nifedipine decreased arterial $P_{O_2}$, did not affect pulmonary artery pressure, and decreased pulmonary vascular resistance because of an increase in cardiac output (Table 2). After nifedipine, there was an increase in the retention-excretion difference for all the inert gases excepted acetone (Fig. 8). This effect was most marked for the inert gases of intermediate solubility and persisted after a "normalization procedure," which consisted in a correction in the recovered inert gas gradients for overall ventilation and blood flow maintained at their initial baseline values. Since an effect of nifedipine on the distribution of ventilation seemed unlikely, the observed deterioration in gas exchange was explained by a nifedipine-induced inhibition of hypoxic vasoconstriction.

However, as seen above, the results of supplemental oxygen studies slightly

**Table 2** Effects of Nifedine Administration on Gas Exchange, Respiratory Mechanics Parameters, and Hemodynamics in Stabilized Patients with ARF on COPD

| | Baseline | Nifedipine | *p* |
|---|---|---|---|
| $Pa_{O_2}$, mmHg | 52 ± 4 | 47 ± 3 | <0.001 |
| $Pa_{CO_2}$, mmHg | 44 ± 3 | 44 ± 3 | NS |
| $P\bar{v}_{O_2}$, mmHg | 31 ± 1 | 32 ± 1 | NS |
| Raw, $cmH_2O/l \cdot s$ | 8.4 ± 1.0 | 10.1 ± 1.1 | NS |
| $\dot{V}_E$, l/min | 8.4 ± 1.0 | 8.7 ± 0.7 | NS |
| $\dot{Q}$, $l/min \cdot m^2$ | 3.1 ± 0.1 | 4.0 ± 0.2 | <0.005 |
| Ppa, mmHg | 33 ± 4 | 32 ± 4 | NS |
| Ppo, mmHg | 3 ± 1 | 4 ± 1 | NS |
| PVR, $dyne \cdot s \cdot cm^{-5} \cdot m^2$ | 803 ± 132 | 581 ± 115 | <0.01 |

*Source*: Ref. 128.

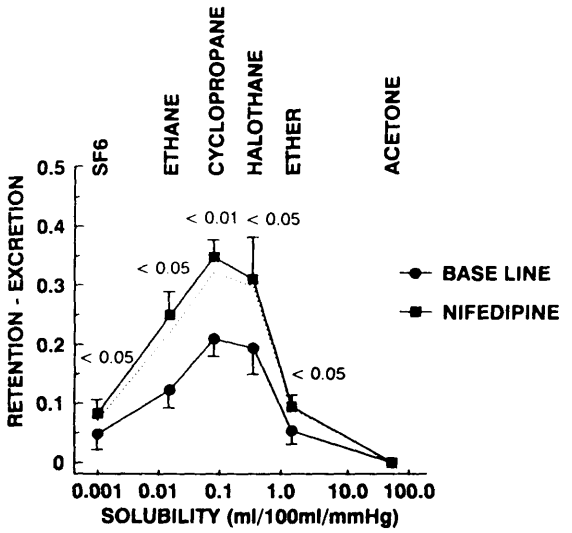


**Figure 8** Mean ± SEM (vertical bars) retention-excretion differences versus solubility for 6 inert gases, before (circles) and after (squares) nifedipine, in 6 patients with COPD. The stippled line indicates the effect of a normalization procedure (i.e. cardiac output and ventilation constrained to pre-nifedipine values) on the differences recovered after nifedipine. All the retention-excretion differences increased excepted for acetone, indicating a deteriorated $\dot{V}/\dot{Q}$ matching in lung units with low as well as with normal $\dot{V}/\dot{Q}$ (After Melot et al.) (128).

support the existence of a strong hypoxic regulation of gas exchange in most patients with COPD. In addition, more recent data on the function of hypoxic vasoconstriction showed no direct relationship between hypoxia-induced increase in pulmonary vascular tone, or lobar flow diversion, and the resulting increase in arterial $P_{O_2}$ (127,128,130). This apparent discrepancy is explained by the shape of the oxyhemoglobin dissociation curve. In fact, the calculated maximum gain due to feedback ($Gfb_{max}$) for hypoxic vasoconstriction in normal man does not exceed 0.6 at an alveolar $P_{O_2}$ around 60 mmHg and falls rapidly off at higher and at lower $P_{O_2}$ (127). Similar estimations have been reported by Grant et al. (129) in the coati mundi, a South American raccoon with a stronger hypoxic pulmonary pressor response than humans. As shown in Figure 8, nifedipine reduced the magnitude of human hypoxic vasoconstriction variably, with a decrease in $Gfb_{max}$ from 0.6 to values between 0.2 and 0.4, still at an alveolar $P_{O_2}$ around 60 mmHg and failing rapidly off at higher and at lower $P_{O_2}$ (127). A Gfb from 0.6 to 0.3 means a 37 to 21% active correction of the change in alveolar $P_{O_2}$ that would occur in a passive system without hypoxic vasoconstriction. For example, if increased perfusion to low $\dot{V}/\dot{Q}$ areas (with a corresponding alveolar $P_{O_2}$ of 60 mmHg) were

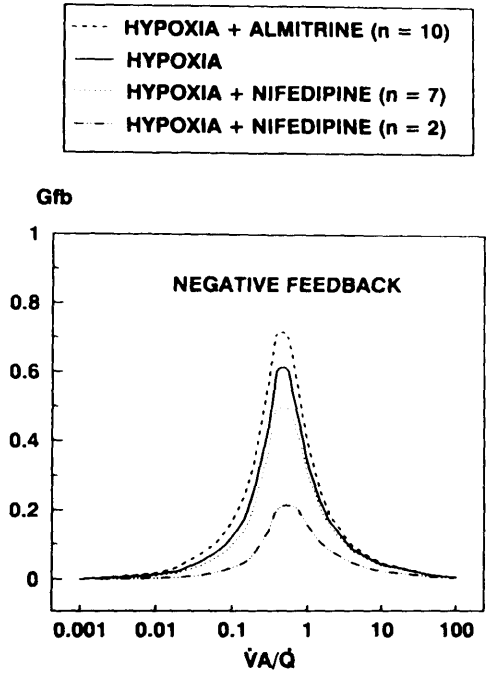


**Figure 9** Gain due to feedback (Gfb) of hypoxic pulmonary vasoconstriction versus $\dot{V}/\dot{Q}$ in normal man at base line (full line, average for 17 subjects) after partial (75 subjects) or total (2 subjects) inhibition of hypoxic vasoconstriction by nifedipine, and after enhancement of hypoxic vasoconstriction by almitrine (10 subjects) (After Melot et al.) (127,130).

to induce a decrease in arterial $P_{O_2}$ by 10 mmHg, this would be limited by hypoxic vasoconstriction to 6 mmHg before nifedipine and to 8 mmHg after nifedipine. On the other hand, alveolar $P_{O_2}$ values around 60 mmHg are obviously higher than in the most diseased lung regions of severely hypoxic patients with decompensated COPD. Inhibition of hypoxic vasoconstriction may be an insufficient explanation for the observed effects of nifedipine on the distribution of $\dot{V}/\dot{Q}$ and on arterial $P_{O_2}$ in patients with decompensated COPD.

Diltiazem is another calcium channel blocker that has been shown to inhibit hypoxic vasoconstriction in experimental animals (125) and tried as a treatment of pulmonary hypertension in COPD (96). Melot et al. (101) investigated the effects of diltiazem, 30 mg/kg given in 30 minutes intravenously, in eight patients with decompensated but stabilized COPD. As shown in Table 3, diltiazem decreased pulmonary vascular tone as assessed by a decrease in pulmonary artery pressures at an unchanged cardiac output but had no effect on arterial blood gases. The retention-excretion differences for the inert gases were unaffected by diltiazem.

**Table 3** Effects of Diltiazem Administration on Gas Exchange, Respiratory Mechanics Parameters, and Hemodynamics in Stabilized Patients with ARF on COPD

| | Baseline | Diltiazem | *p* |
|---|---|---|---|
| $Pa_{O_2}$, mmHg | 41 ± 2 | 43 ± 2 | NS |
| $Pa_{CO_2}$, mmHg | 48 ± 3 | 48 ± 3 | NS |
| $P\bar{v}_{O_2}$, mmHg | 28 ± 1 | 30 ± 1 | NS |
| Raw, $cmH_2O/l \cdot s$ | 7.7 ± 2.5 | 7.9 ± 2.2 | NS |
| $\dot{V}_E$, l/min | 9.4 ± 0.7 | 9.3 ± 0.8 | NS |
| $\dot{Q}$, $l/min \cdot m^2$ | 3.8 ± 0.2 | 3.8 ± 0.3 | NS |
| Ppa, mmHg | 36 ± 4 | 33 ± 3 | NS |
| Ppo, mmHg | 7 ± 2 | 8 ± 1 | NS |
| PVR, $dyne \cdot s \cdot cm^{-5} \cdot m^2$ | 637 ± 99 | 541 ± 80 | <0.05 |

*Source*: Ref. 101.

Thus, a reduction in pulmonary vascular tone does not necessarily decrease gas exchange.

Prostaglandin $E_1$ is a potent pulmonary vasodilator used as an acute intravenous treatment in a variety of pulmonary hypertensive states (131). At doses of up to 0.04 μg/kg/min, this vasodilating prostaglandin does not inhibit hypoxic vasoconstriction in normal humans (132). Doses 10 times higher are needed to inhibit hypoxic pulmonary vasoconstriction in dogs (133). Prostaglandin $E_1$ at 0.02–0.04 μg/kg/min has been reported to decrease pulmonary artery pressures and resistance in patients with decompensated COPD (132). Melot et al. (101) investigated the effects of prostaglandin $E_1$ at 0.02–0.04 μg/kg/min on gas exchange in patients stabilized after admission for decompensated COPD. As shown in Table 4, prostaglandin $E_1$ decreased arterial $P_{O_2}$, pulmonary artery pressures, pulmonary vascular resistance, and airway resistance and increased cardiac output. There was an increase in the retention-excretion difference for the gases with intermediate solubility, indicating a deterioration in $\dot{V}/\dot{Q}$ matching in lung units with lower than normal $\dot{V}/\dot{Q}$. This effect was still significant after a normalization procedure (Fig. 10). Here again, separate determinations of the distributions of ventilation and perfusion before and after prostaglandin $E_1$ would be helpful to determine the role of inhibited hypoxic vasoconstriction, if any, and bronchodilation in the observed deterioration in gas exchange.

### *Vasoconstrictors*

Almitrine is a peripheral chemoreceptor agonist that has been shown, at doses not associated with a detectable change in ventilation, to improve arterial blood gases in stable as well as in decompensated COPD (81). Melot et al. (101) investigated

**Table 4** Effects of Prostaglandin $E_1$ Administration on Gas Exchange, Respiratory Mechanics Parameters, and Hemodynamics in Stabilized Patients with ARF on COPD

| | Baseline | Prostaglandin $E_1$ | *p* |
|---|---|---|---|
| $Pao_2$, mmHg | 61 ± 2 | 56 ± 2 | <0.001 |
| $Paco_2$, mmHg | 46 ± 2 | 46 ± 2 | NS |
| $P\bar{v}O_2$, mmHg | 34 ± 1 | 35 ± 1 | NS |
| Raw, $cmH_2O/l \cdot s$ | 6.2 ± 0.7 | 4.6 ± 0.5 | <0.05 |
| $\dot{V}_E$, l/min | 9.5 ± 0.8 | 9.3 ± 0.7 | NS |
| $\dot{Q}$, $l/min \cdot m^2$ | 3.3 ± 0.2 | 3.9 ± 0.3 | <0.01 |
| Ppa, mmHg | 23 ± 1 | 19 ± 3 | <0.001 |
| Ppo, mmHg | 5 ± 1 | 4 ± 1 | NS |
| PVR, $dyne \cdot s \cdot cm^{-5} \cdot m^2$ | 447 ± 34 | 311 ± 19 | <0.001 |

*Source*: Ref 101.

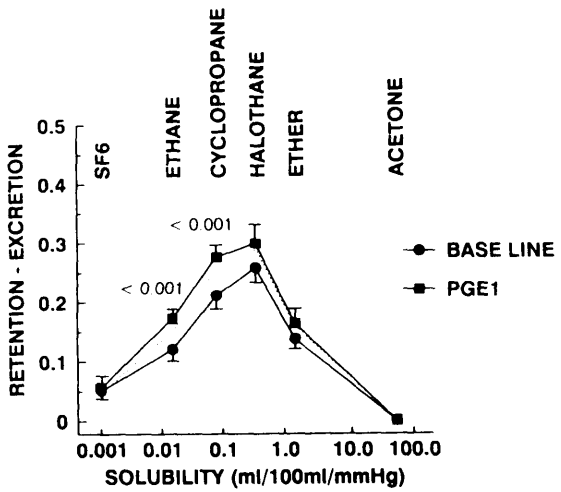


**Figure 10** Mean ± SEM (vertical bars) retention-excretion differences versus solubility for 6 inert gases, before (circles) and after (squares) prostaglandin $E_1$, in 12 patients with COPD. The stippled line indicates the effect of a normalization procedure (i.e. cardiac output and ventilation constrained to pre-prostaglandin $E_1$ values) on the differences recovered after prostaglandin $E_1$. The retention-excretion differences increased for ethane and for cyclopropane, indicating a deteriorated $\dot{V}/\dot{Q}$ matching in lung units with a low $\dot{V}/\dot{Q}$ (After Melot) (130).

**Table 5** Effects of Almitrine Administration on Gas Exchange, Respiratory Mechanics Parameters, and Hemodynamics in Stabilized Patients with ARF on COPD

| | Baseline | Almitrine | *p* |
|---|---|---|---|
| $Pa_{O_2}$, mmHg | 42 ± 4 | 59 ± 3 | <0.01 |
| $Pa_{CO_2}$, mmHg | 46 ± 3 | 43 ± 3 | <0.05 |
| $P\bar{v}_{O_2}$, mmHg | 31 ± 1 | 32 ± 1 | NS |
| Raw, $cmH_2O/l \cdot s$ | 6.2 ± 0.9 | 7.8 ± 1.3 | NS |
| $\dot{V}_E$, l/min | 11.2 ± 0.1 | 10.4 ± 0.6 | NS |
| $\dot{Q}$, $l/min \cdot m^2$ | 3.1 ± 0.1 | 3.0 ± 0.2 | NS |
| Ppa, mmHg | 28 ± 5 | 32 ± 5 | NS |
| Ppo, mmHg | 5 ± 1 | 5 ± 1 | NS |
| PVR, $dyne \cdot s \cdot cm^{-5} \cdot m^2$ | 607 ± 133 | 752 ± 142 | <0.05 |

*Source*: Ref. 101.

gas exchange by MIGT in six patients with decompensated but stabilized COPD before and after administration of 100 mg almitrine orally. Almitrine increased arterial $P_{O_2}$ and pulmonary vascular resistance and decreased arterial $P_{CO_2}$ (Table 5). The retention-excretion difference decreased for the inert gases with intermediate solubility, indicating an improved $\dot{V}/\dot{Q}$ matching in low $\dot{V}/\dot{Q}$ units (Fig. 11). Similar observations had been reported earlier by Castaing et al. (18). Since almitrine has not been found by independent methods to affect the distribution of ventilation in normal humans (134) or in patients (135), these results were tentatively explained by an almitrine-induced enhancement of hypoxic pulmonary vasoconstriction. However, Melot et al. (136) found that almitrine indeed slightly enhanced hypoxic vasoconstriction in humans, but that this effect was associated with an increased Gfb from 0.59 to only 0.65, and still limited to an alveolar $P_{O_2}$ around 60 mmHg, falling off at higher and at lower $P_{O_2}$. A Gfb increase from 0.59 to 0.65 corresponds to an active correction of a decreased alveolar $P_{O_2}$ by a maximum of 37 to 39%, which can only have slight consequences on the composition of arterial blood gases. Interestingly, De Backer et al. (137) reported that almitrine does not improve arterial oxygenation in patients with COPD after bilateral carotid body resection, supporting the hypothesis that slight changes in the distribution of ventilation, beyond the resolution of until now used isotopic methods, may account for observed changes in low $\dot{V}/\dot{Q}$ units after almitrine, even in conditions of controlled ventilation (115,135).

## IV. Conclusion

The determinants of arterial $P_{O_2}$ are numerous: mixed venous $P_{O_2}$ and $P_{CO_2}$, $\dot{V}/\dot{Q}$, $\lambda_{O_2}$, and $\lambda_{CO_2}$. Mixed venous composition is itself a function of several factors.

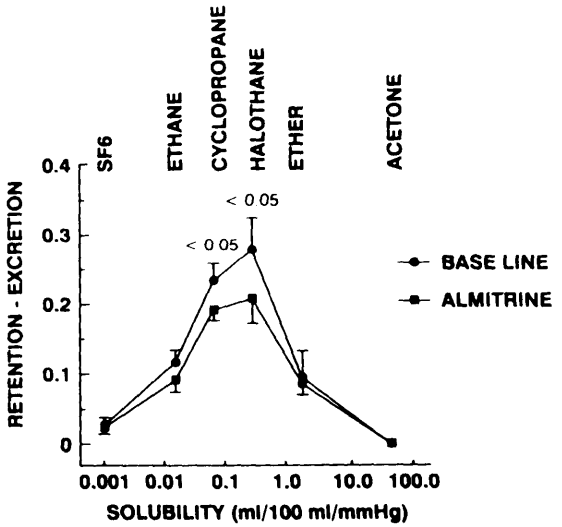


**Figure 11** Mean ± SEM (vertical bars) retention-excretion differences versus solubility for 6 inert gases, before (circles) and after (squares) almitrine in 6 patients with COPD. The retention-excretion differences increased for cyclopropane and for halotane, indicating a deteriorated $\dot{V}/\dot{Q}$ matching in lung units with a low and with low-normal $\dot{V}/\dot{Q}$ (After Melot et al.) (134).

Therefore, when many of these determinants or factors are unknown, the interpretation of a gas exchange alteration could be misleading. The concept of hypoventilation should be restricted either to a well-measured decrease in ventilation in a patient remaining in steady condition of $\dot{V}/\dot{Q}$ heterogeneity or to a lack of response of the patient's respiratory system to a chemical stimulus. The term hypercapnia, which makes no inference to an underlying mechanism, seems more appropriate.

The alterations in gas exchange induced by mechanical ventilation or drugs are often due to both perfusion and ventilation disturbances. In most cases it appears that no clear-cut conclusion can be made about the respective influence of these disturbances on gas exchange. Therefore, more precise experimental procedures or techniques are needed in spite of the introduction in the late 1970s of the MIGT.

Studying gas exchange in the acute state of a disease is not easy, which would explain why most of the measurements reported upon here have been performed in patients recovering from ARF. Even the effect upon gas exchange of some drugs, like diuretics (138), remains poorly understood or speculative in the ARF situation; therefore, more clinical studies would be useful. Gas exchange is

the major function of the lung, and although it depends on numerous interrelated factors, the mechanisms that alter this crucial function in ARF patients with COPD should continue to be of considerable interest in the coming years.

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# 9

# Heart–Lung Interactions in Chronic Obstructive Pulmonary Disease

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## I. Introduction

The primary goal of the respiratory and cardiovascular systems is to supply adequate amounts of oxygen to the tissues to meet their metabolic demand and to excrete the carbon dioxide correspondingly produced. Pulmonary vascular disease is a common and potentially serious complication of COPD, and it is currently well recognized that heart-lung interactions in this setting are responsible for right ventricular (RV) dysfunction. The latter adds to the consequences of airflow obstruction on pulmonary gas exchange to impair oxygen delivery (1).

From a clinical and epidemiological point of view, the consequences of COPD on right heart function have long been described and their importance recognized. The definition of the chronic form of cor pulmonale is "an alteration in structure or function of the RV resulting from a disease affecting structure or function of the lung or its vasculature, except when this alteration results from a disease of the left side of the heart or congenital heart disease" (2). Acute cor pulmonale is defined as right heart strain or overload resulting from acute pulmonary hypertension (3). The major cause of chronic cor pulmonale is COPD, chronic obstructive bronchitis, or emphysema. However, the precise prevalence of cor pulmonale in COPD remains uncertain. It has been estimated that approximately

50% of patients with COPD older than 50 years of age will develop pulmonary hypertension. When present, RV dysfunction reduces exercise tolerance, increases dyspnea, and contributes to an overall decrease in functional status. Survival rates from COPD when pulmonary vascular resistance is greater than 550 dynes·s·cm$^{-5}$ approximate those of inoperable lung cancer (4). COPD annually accounts for at least 50,000 deaths in the United States: one half might be expected to be associated with anatomical evidence of cor pulmonale at autopsy (5). Cor pulmonale resulting from COPD is responsible for 10–30% hospital admissions for congestive heart failure in the United States (6). Thus, by contributing to an already compromised oxygen delivery system, pulmonary vascular disease in this setting affects not only survival but also quality of life. It is important to emphasize that its early recognition and treatment may lead to prolonged survival and improved quality of life (7).

From a pathophysiological point of view, the right ventricle has long been considered as simply a conduit for blood flow between the peripheral venous circulation and the pulmonary arterial tree (8). It was overshadowed by its muscular, thick-walled neighbor, the left ventricle (LV). Mainly because of observations of acute cor pulmonale leading to circulatory shock, the physiological role of the RV systole has now been revisited, and this renewed interest is closely associated with the contemporary scrutiny of heart-lung interactions and ventricular interdependence. The last 20 years have witnessed a growing awareness that RV dysfunction may play a pivotal role in some of the most frequently encountered cardiopulmonary disorders associated to pulmonary artery hypertension, and particularly acute exacerbations of COPD. In COPD patients with acute respiratory failure (ARF), a marked increase in RV afterload develops, which results in increased RV volume, wall stress, and myocardial oxygen consumption. If severe enough, these changes may lead to a decline in cardiac output. Since, during critical illness, maintenance of the cardiac output may depend on RV function, the clinician needs to be able to discern the presence of RV dysfunction and whether this decreased RV performance is or is not due to decreased ventricular filling, increased RV afterload, decreased contractile state via myocardial ischemia, or the combination of two or even three of these mechanisms (9).

This chapter will discuss functional and structural changes, clinical aspects, and therapeutic implications in COPD-related cor pulmonale within the integrated framework of cardiopulmonary interactions.

## II. Pathophysiology of Heart-Lung Interactions in COPD

### A. RV Response to Acute and Chronic Pulmonary Hypertension

Low resistance is the main physical characteristic of the normal pulmonary circulation. Both RV anatomy and functional properties are adequate to work

against these normal physical constraints, but they highlight the inability of the RV to face an acute increase in pulmonary resistance as may occur in acute exacerbations of COPD.

### *RV Physiology*

Interventricular SeptumThe RV wall is normally thinner than the LV wall, but may become nearly as thick with adaptation to chronic pulmonary hypertension. The normal contraction of the interventricular septum mainly acts to decrease LV diameter and causes the septum to bulge into the RV cavity. The position of the septum also depends on the transseptal pressure gradient throughout the cardiac cycle, and marked displacements may occur depending on the respective left and right intrachamber pressures (10). Increased RV pressure results in a leftward septal displacement that further reduces the apparent LV compliance and may be responsible for a decrease in LV stroke volume. This displacement is of less magnitude in systole than in diastole because of the different myocardial stiffness during the cardiac cycle.

#### Role of the RV Free Wall

Early experiments in which cauterizing the RV free wall produced no change in RV pressures (8) suggested that RV function was not significantly impaired by selective RV free wall destruction. This can be explained by the fact that the RV and LV are mechanically coupled (11): by virtue of their anatomic continuity, tension developed during contraction of the intact LV is transmitted to the damaged RV wall, preserving RV pump function (12). However, acute and complete elimination of RV function does lead to a marked fall in cardiac output (13), which can be restored to the initial level by means of aggressive volume expansion. The cost of this result is a marked elevation in central venous pressure: thus, the normal role of the RV seems to be to maintain a low systemic venous pressure.

#### Dynamics of the RV Contraction

The RV is embryologically, anatomically, and functionally divided into sinus (inflow) and conus (outflow) regions (14). RV contraction proceeds sequentially from the sinus to the conus. During the sinus contraction, the conus dilates concomitantly with the initial part of the pulmonary artery, acting as a reservoir (15). Under physiological conditions, the conus contracts 25–50 msec after the sinus and remains contracted when the inflow tract relaxation begins. Rather than a booster, the RV contraction has been compared to a peristaltic movement, initiated by the atrial systole (16). When the RV ejection is impeded by acute pulmonary hypertension, the functional difference between inflow and outflow tract persists (17). It may be assumed that this sinus-conus asynchronism helps to protect pulmonary arteries from high peaks of pressure and to promote a continuous blood flow in the pulmonary vessels for optimal gas exchanges.

## Structural and Functional Changes in RV Pressure Overload

Preparations of isolated contracting intact heart make possible the study of the effects of acute changes in afterload on RV performance independent of changes in preload. In contrast, in the clinical setting, abnormalities in RV preload and afterload often coexist in the same patient. For instance, in patients with primary pressure overload states such as acute exacerbations of COPD, volume overload occurs as a consequence of the inability of RV to sustain systolic performance. These interactions between RV preload and afterload should always be kept in mind when properly interpreting data derived from intact animal models and in the clinical setting (18).

### Configurational Changes

Specific configurational changes in the presence of RV pressure overload are less well described than in the presence of RV volume overload, because of the constant coexistence of pressure and volume overload in such circumstances. The RV pressure increases and may compete with the LV pressure to position the interventricular septum (19). The systolic leftward septal shift optimizes the mechanical effect of the RV contraction (9).

Changes in the configuration of both ventricles have been observed during acute RV pressure loading in dogs. Following acute pulmonary artery constriction, the LV septal-free wall dimension and shortening are reduced as is its contribution to the global LV systolic function (20), whereas in chronic RV pressure overload, the LV septal-free wall dimension and shortening are maintained (21). At least two mechanisms contribute to this leftward shift of the ventricular septum: competition between both ventricles inside an inextensible pericardial cavity and series interactions with decreased LV filling due to a reduced RV stroke volume. Since the absence of pericardium has been shown to be of little influence in ventricular interdependence in a canine model, the series interactions mechanism may predominate when the RV is afterloaded (22).

### Functional Changes and Contractile Properties

To what extent the contractile properties of the RV myocardium are altered by chronic pressure overload remains uncertain. Indeed, although the ventricular response to chronic pressure overload has been extensively studied in animals, the available data are somewhat conflicting. When interpreting such data, special attention must be given to the species studied, the magnitude of the hypertrophy produced, and the duration of the applied pressure load (18).

In most cases, RV and LV hypertrophy was produced by constriction of the pulmonary artery and aorta, respectively. In the case of RV overload, the ventricle–to–body weight ratio increased by 44–90%, while in the case of LV pressure overload, the hypertrophy remained modest (30–40%) (23). In most

studies, the maximum active tension developed by the hypertrophied papillary muscles, the time derivative of tension development (dT/dt), and the maximum measured velocity of shortening ($V_{max}$) were reduced. The time to peak tension, a measure of the duration of active state, was either normal or, more frequently, prolonged. The rate at which the pressure load is applied to the ventricle does not appear to influence these mechanical changes, since the same findings have been observed in models where the pressure load was gradual and in models where it was abrupt (24).

Williams and Potter (25) examined the long-term effects of chronic pressure overload and compared the mechanical characteristics of hypertrophied cat RV. At 6 weeks, they observed that maximum active tension, dT/dt, and $V_{max}$ were depressed and that time to peak tension was prolonged. By contrast, none of these abnormalities could be demonstrated at 24 weeks. The magnitude of hypertrophy was the same at both time points. Similar results were previously reported in rabbits for the LV by Williams and Potter (25). In this study, again with comparable degrees of hypertrophy, contractile indices 9 and 40 days after pulmonary artery constriction were depressed, whereas they were normal after 96 days. Interestingly, ejection phase indices of systolic performance in the intact RV correlated poorly with the findings in isolated papillary muscles, suggesting that global compensatory mechanisms in intact animals mask the intrinsic functional abnormalities of the hypertrophied heart muscle.

In clinical studies of chronic RV pressure overload, decreased ejection fraction is frequently present in line with the systolic load, but abnormalities in RV contractility are generally absent (26).

To sum up, the early functional response to pressure overload of the RV is a reduction in the intrinsic velocity of the contractile apparatus, associated with a compensatory prolonged duration of force development. In the intact organism, these defects may be masked by neurohumoral effects and are not easily detected by clinical indices of systolic pump function. With sustained pressure overload, there is good evidence that these mechanical abnormalities may revert towards normal. However, further depression of contractile function during prolonged and severe pressure overload is demonstrated in isolated heart muscle (27).

### *Response of Right Coronary Circulation to RV Overload*

#### Characteristics of the RV Coronary Circulation

The RV is mainly perfused by the right coronary artery. Relative to the myocardial mass, the subendocardial coronary vasculature of the RV is less developed than it is in the LV. However, the RV coronary perfusion is easily maintained during both systole and diastole because of an always positive driving pressure. Indeed, the driving pressure across the RV coronary circulation is the difference between the intracoronary pressure, which equals the aortic pressure on the one hand, and the

right myocardial tissue pressure, which can be estimated by the intracavity pressure on the other hand.

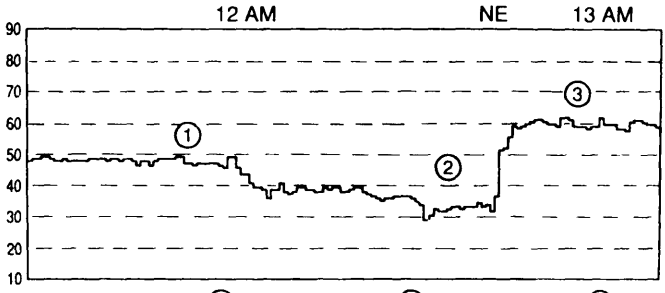
As for LV, the RV myocardial oxygen extraction is nearly maximal: venous $P_{O_2}$ ranges from 18 to 20 mmHg (28). Meeting an increased RV oxygen requirement therefore requires an augmentation of coronary blood flow. This is mostly obtained by coronary vasodilatation, which can be mediated by several metabolic factors including adenosine monophosphate (29). The total RV amount of high-energy phosphate is lower than in the LV. This could explain a particular sensitivity to hypoxia.

### Possible Mechanisms for RV Ischemia

First, increased afterload can increase myocardial oxygen consumption. For the LV, a close relationship has been demonstrated between myocardial oxygen consumption and the total pressure volume area, determined by both systolic and diastolic pressure volume lines and the portion of the pressure volume loop from end-diastole to end-systole. Because of methodological difficulties in measuring its oxygen consumption, no such data are available for the RV. However, experimental results support the hypothesis of an increased RV myocardium oxygen demand in acute pressure overload (30). It has been shown that pressure work requires more energy than volume work (31).

Second, RV ischemia can result from a decrease in the systolic coronary perfusion driving pressure, even in the absence of significant coronary disease. Such a mechanism has been hypothesized in many other pathological circumstances. It is likely to occur, and consequently to impair RV contractility, when acute pulmonary hypertension coexists with reduced systemic pressure (32). In canine models of pulmonary hypertension, Scharf et al. (33) have actually found that increasing aortic pressure improved RV performance. They could, however, not demonstrate global RV ischemia and speculated that the improved performance was due to an increased perfusion of the deeper layers of the RV myocardium. These results suggest that RV ischemia is not indispensable for RV failure to occur in acute pulmonary hypertension. Therefore, in patients without coronary disease, advocating RV ischemia to explain decreased RV contractility is probably justified only in extreme situations (Fig. 1).

Third, hypertrophied hearts may have a particular sensitivity to hypoxia that could be clinically relevant (34). Indeed, whereas the coronary blood flow per unit of muscle weight is normal in hypertrophied hearts, coronary vascular resistance is higher than in normal myocardium and a greater proportion of the total vasodilation reserve is used to maintain resting flow (35). An important expression of this defect has been the finding of a disproportionate decrease in the endocardial to epicardial flow ratio in hypertrophy during the stress of pacing and during exercise (36). Most of these data come from models of LV hypertrophy, but a reduced vasodilatory response has actually been observed in dogs with RV hyper-




| | ① | ② | ③ |
|---|---|---|---|
| RAP | 12 | 20 | 15 |
| PWP | 8 | 12 | 13 |
| CI | 2.5 | 2.0 | 3.3 |
| RVEDV | 120 | 168 | 125 |
| RVEF | 25 % | 17 % | 34 % |
| MAP | 50 | 55 | 73 |

**Figure 1** Continuous central venous oximetry tracing ($Svo_2$) from a COPD patient with pulmonary embolism. (1) The acute increase of RV afterload leads to both RV failure and severe hypotension. (2) Despite volume loading and consequent increase in RV diastolic volume and pressure, circulatory shock occurs. (3) Norepinephrine infusion is only able to increase systemic arterial pressure and hence coronary perfusion pressure. Consequently RV function improves and circulatory shock disappears. RAP = right atrial pressure (mmHg); PWP = pulmonary wedge pressure (mmHg); CI = cardiac index (L/min.m$^2$); RVEDV = right ventricular end-diastolic volume (mL/min.m$^2$); RVEF = right ventricular ejection fraction; MAP = mean systemic arterial pressure (mmHg).

trophy (36) and in the RV of patients with atrial septal defects and pulmonary hypertension (37).

### B. Pulmonary and Systemic Hemodynamics in COPD

#### *Pathogenesis of Pulmonary Hypertension in COPD*

Although there is no universally accepted definition for pulmonary hypertension, the hemodynamic criteria for entry into the National Institutes of Health Registry on Primary Pulmonary Hypertension included a mean pulmonary artery pressure (PAP) greater than 25 mmHg at rest or 35 mmHg on exercise (38). Pulmonary hypertension in patients with COPD may arise from a variety of causes that contribute to its development and maintenance, of which alveolar hypoxia is the most significant. There is an inverse correlation between the hemodynamic severity of pulmonary hypertension and the degree of arterial hypoxemia (39). Moreover, several studies have demonstrated a significant relationship between the decline in arterial oxygen tension and the progression of pulmonary hypertension

(40). The mechanism responsible for hypoxic pulmonary vasoconstriction remains incompletely understood, but it appears that this phenomenon is an intrinsic property of pulmonary vascular smooth muscle cells. Sustained exposure to hypoxia eventually leads to pulmonary vascular remodeling, characterized by medial hypertrophy and luminal narrowing.

The incomplete hemodynamic response to long-term oxygen therapy in hypoxemic patients with COPD (41) suggests that other factors also contribute to pulmonary vascular disease in this setting. Hypercapnia and metabolic acidosis potentiate the hypoxic pressor response in animals, and these abnormalities may contribute to the maintenance of pulmonary vascular disease in some patients. Anatomical reduction in the cross-sectional area of the pulmonary vascular bed may result either from structural narrowing of vessels induced by chronic hypoxia, from the development of Zone II conditions as a result of compression of the vasculature (42), or from direct destruction of vessels, as occurs in emphysema (43). Hyperviscosity resulting from polycythemia in chronically hypoxic patients may also contribute to increased pulmonary vascular resistance. Elevated cardiac output, increased pulmonary blood volume, and auto-PEEP may aggravate pulmonary hypertension in COPD (44). Although LV dysfunction is excluded by definition as a primary cause of cor pulmonale, elevated pulmonary venous pressure nevertheless does exacerbate pulmonary hypertension in some COPD patients with either marked RV dilation-induced alteration of LV compliance (ventricular interdependence) or primary LV dysfunction. The inability to recruit vessels or dilate the existing vasculature initially results in increases of both PAP and cardiac output during exercise. Subsequently, the aforementioned factors contribute to the persistence of pulmonary hypertension at rest. Overt RV failure, resulting from the sustained increase in RV work, may eventually develop.

### *Natural History of Untreated Pulmonary Hypertension in COPD*

Pulmonary hypertension slowly increases with time in COPD patients with mild to moderate hypoxemia (40,45,46). For example, Weitzenblum et al. (40) followed up 93 COPD patients over about 8 years. The use of vasodilators and long-term oxygen therapy was not permitted. Two groups were defined according to initial mean pulmonary artery pressure (mPAP). Sixty-one patients (group 1) had no pulmonary hypertension at entry (mPAP $< 20$ mmHg), with a mean $Pa_{O_2}$ of $67 \pm 7$ mmHg. Thirty-two patients (group 2) had initial pulmonary hypertension (mPAP $> 20$ mmHg) with a slightly lower mean $Pa_{O_2}$ ($62 \pm 7$ mmHg). Changes in mPAP were minor during the study period, and no significant change in cardiac output or RV-filling pressures were seen in either group. However, an increase of mPAP of $\geq 5$ mmHg was observed in a subgroup of 27 patients. These patients did not differ from the others with respect to clinical characteristics, spirometry, $Pa_{O_2}$, and initial mPAP but showed a significant deterioration in $Pa_{O_2}$ and $Pa_{CO_2}$ ($66 \pm 8$

to 59 ± 9 mmHg, and 37 ± 3 to 46 ± 7 mmHg, respectively; $p < 0.01$) during the study period. This suggests that hypoxemia is an important factor in the progression of pulmonary hypertension in COPD. This finding was confirmed by the observed rapid rise in mPAP in untreated patients participating in the British Medical Research Council study of controlled oxygen (47). It should be noted that these patients were more severely hypoxemia ($Pao_2$ = 40–60 mmHg) than those studied by Weitzenblum et al.

By contrast, Kawakami et al. (48) reached the conclusion that hypoxia reduced survival through mechanisms other than those related to cor pulmonale. Indeed, among the 50 patients with COPD who were followed up after 4 years, the nonsurvivors ($n$ = 27) had a lower $Pao_2$ and $Pvo_2$ at study entry, but no difference in initial mPAP, RV work, oxygen transport, or oxygen extraction ratio when compared to survivors. Relatively few patients were enrolled in this study, and longitudinal hemodynamic data were not evaluated. As pointed out by Tockman et al. (49), the small size of the patient population limited the power of this study to detect significant differences between survivors and nonsurvivors. Moreover, the absence of hemodynamic follow-up made a potential progression of pulmonary hypertension or changes in oxygen delivery impossible to assess. Hypoxic pulmonary vasoconstriction, pulmonary hypertension, and cor pulmonale remain generally accepted risk factors in the prognosis of COPD (40,49,50).

### *Oxygen Delivery Adaptation in COPD*

Although cor pulmonale is often viewed as a form of heart failure, cardiac output is often normal or slightly elevated in patients with COPD until shortly before death (4,51,52). In the study by Kawakami et al. (48), although both survivors and nonsurvivors had initial high cardiac output, a trend toward lower cardiac output appeared in the nonsurvivors group.

Such maintenance of oxygen delivery may be achieved by an increase in cardiac output or in arterial oxygen content (polycythemia). The hemodynamic consequences of these different compensatory mechanisms are illustrated by the study by Tenney and Mithoefer (53), which reported wide interindividual variations in oxygen delivery and mixed venous oxygenation. For a given oxygen delivery, patients with a higher cardiac output had a higher venous oxygen content than those with a relatively low cardiac output and polycythemia—pulmonary hemodynamics and coefficient of oxygen delivery being otherwise similar, Kawakami et al. (48) observed that prognosis was poorer in the group of patients who had the lowest values of mixed venous saturation. Thus, taking into account the information of Tenney and Mithoefer (53), the development of polycythemia in COPD to maintain oxygen delivery in the face of chronic hypoxia does not necessarily represent a successful long-term adaptation. Because increased cardiac output is crucial in the maintenance of mixed venous oxygenation, and

although Kawakami et al.'s data (48) did not point to the importance of cardiac output by itself, Wiedemann and Matthay (54) advanced the hypothesis that failure to increase cardiac output in face of significant venous hypoxemia is a crucial maladaptation that could adversely affect survival.

Controversial data in the literature about the relationship between oxygen delivery and oxygen consumption in patients with COPD make it difficult to accept or reject this hypothesis. In normal subjects, oxygen consumption does not change with variations in oxygen delivery, unless the latter becomes severely reduced (55). Early studies suggested that in COPD patients the relationship between oxygen consumption and oxygen delivery might be abnormal and analogous to that observed in some ARDS and septic patients (56,57). Indeed, Brent et al. (58) demonstrated that oxygen consumption was directly related to oxygen delivery in a group of COPD patients in whom cardiac output was acutely altered by pharmacological agents, namely, hydralazine to increase it or nitroprusside to decrease it. Because the vasodilators used might have affected tissue metabolism or peripheral vasoregulation, Albert et al. (59) reinvestigated this relationships, this time using a nonpharmacological method (passive leg elevation) to alter cardiac output. Consistent with earlier reports, the results of this study suggested that in these patients aerobic metabolism becomes limited by oxygen supply at normal or even increased levels of oxygen delivery, with a relatively fixed oxygen extraction when oxygen delivery falls. This abnormal relationship between oxygen consumption and oxygen delivery has been termed pathological supply dependency (56).

This concept was first challenged by Chappell et al. (60), who found that changes in oxygen delivery were not followed by predictable alterations in oxygen consumption. Two categories of arguments have been raised against the concept of oxygen supply dependency. The first one deals with the observation that oxygen supply dependency has been described in quite different groups of patients, including not only COPD patients, but also patients with ARDS, pneumonia, or congestive heart failure (61). Therefore, it has been suggested that the dependency of oxygen consumption and oxygen delivery is not "pathological" but represents the "normal" relationship in humans. This could illustrate interspecies differences: in the presence of decreased oxygen delivery, humans might be unable to achieve tissue oxygen extraction as efficiently as is observed in anesthetized animals. The second category of arguments deals with methodological issues. An important weakness of most previous clinical studies (62–64) is that oxygen consumption and oxygen delivery were calculated from a common set of measured variables, namely, cardiac output and arterial blood oxygen content. Consequently, the observed oxygen supply dependency might be artefactual, resulting from pure mathematical coupling (65). Despite the demonstration that the correlation observed in some of these studies between oxygen consumption and oxygen delivery was too strong to be ascribed only to mathematical coupling (66), it

should be noted that studies escaping the criticism of shared variables by using independent methods to measure oxygen consumption and oxygen delivery failed to demonstrate $O_2$ supply dependency (67–73). To conclude, there is no firm evidence of pathological oxygen supply dependency in COPD patients. As a consequence, analysis of the oxygen delivery and oxygen consumption relationship is not useful for guiding therapy in acute or chronic cor pulmonale.

### C. Influence of Breathing Conditions on Cardiac Function

The heart and great vessels are located inside the thorax and are exposed to the influence of the organs of respiration. Basically, two types of respiratory changes occur that influence cardiac function: lung volume changes and intrathoracic pressure changes.

#### *Respiratory Influence on Venous Return*

Guyton (74) has analyzed the factors that influence the return of blood from the periphery to the right atrium. The classical venous return curve (Fig. 2) characterizes the relationship between right atrial pressure and venous return, which is equal to cardiac output in the steady state. As right atrial pressure (the back pressure to inflow of blood into the thorax) increases, venous return decreases

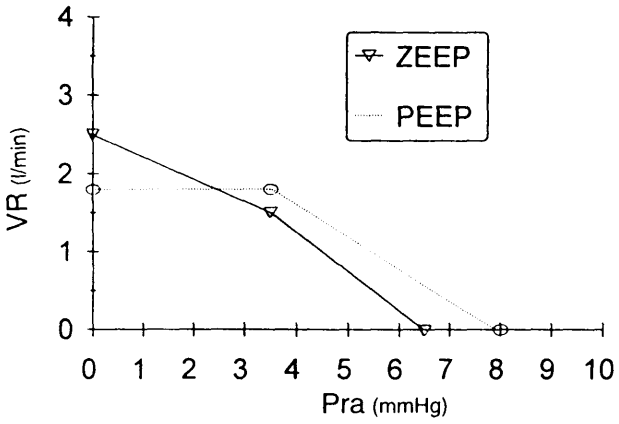



**Figure 2** A venous return curve in a single animal before (ZEEP) and during ventilation with PEEP. Note that with PEEP, there is an increase in mean circulatory pressure (Pra at VR = 0), and the point on the curve at which maximum flow occurs is at a higher Pra. As long as Pra is higher than this point, VR is increased with PEEP at any given Pra. At lower Pra's, however, VR may be less. VR = venous return; Pra = right atrial pressure. (From Ref. 75.)

until flow ceases. At this point, right atrial pressure is equal to the peripheral venous pressure driving blood toward the heart (the mean circulatory pressure). Conversely, as right atrial pressure decreases, venous return rises until it reaches a maximum value when right atrial pressure reaches a slightly negative value. The phenomenon of flow limitation is due to collapse of the great veins at the entrance to the thorax.

### *Effects of RV and LV Function*

Two events occur during spontaneous inspiration: pleural pressure decreases and lung volume increases. Since the decrease in pleural pressure tends to enhance venous return into the chest, increases in RV end-diastolic transmural pressure and volume are observed. As the result of the increase in RV preload, pulmonary arterial flow increases during inspiration (76). Increases in lung volume also affect the state of the pulmonary vasculature. At low volumes, below functional residual capacity, increases in lung volume tend to dilate pulmonary vessels, whereas at higher lung volumes they are constricted (77). The sum of these effects is that during spontaneous inspiration little change in the pulmonary arterial transmural pressure, a measure of RV afterload, is seen (78).

RV dilation during inspiration leads to stiffening of the LV, the presence of the pericardium greatly enhancing this ventricular interdependence (12). It is well known that, in contrast to the rise in RV output that occurs with spontaneous inspiration, LV output falls. This is associated with an increase in filling pressure while LV diastolic volume decreases due to the dilated RV. As evidenced in a preparation in which the RV was bypassed, this is not the only mechanism that impedes the output of blood from the LV during inspiration (79). First, decreases in pleural pressure can be transmitted directly to the aorta, and consequently the pressure gradient for flow from intrathoracic to extrathoracic arteries is reduced. Second, aortic transmural pressure actually rises. This is functionally equivalent to raising LV afterload. There is strong evidence that decreases in pleural pressure when sustained or exaggerated can act similarly to an afterload placed on the LV (Fig. 3).

### *Phasic Changes of RV Function During COPD*

#### Inspiratory Impairment of RV Function During Acute Exacerbations of COPD

*Phasic Changes in RV Ejection Fraction.* COPD patients with respiratory failure, breathing spontaneously, exhibit a marked increase of pulmonary vascular resistance associated with a cyclic modulation of RV loading conditions due to changes in pleural pressure throughout the respiratory cycle. To assess RV function in such patients, Dhainaut and Brunet (81) performed simultaneous bedside right heart catheterization and two-dimensional (2D) echocardiography. The ther-

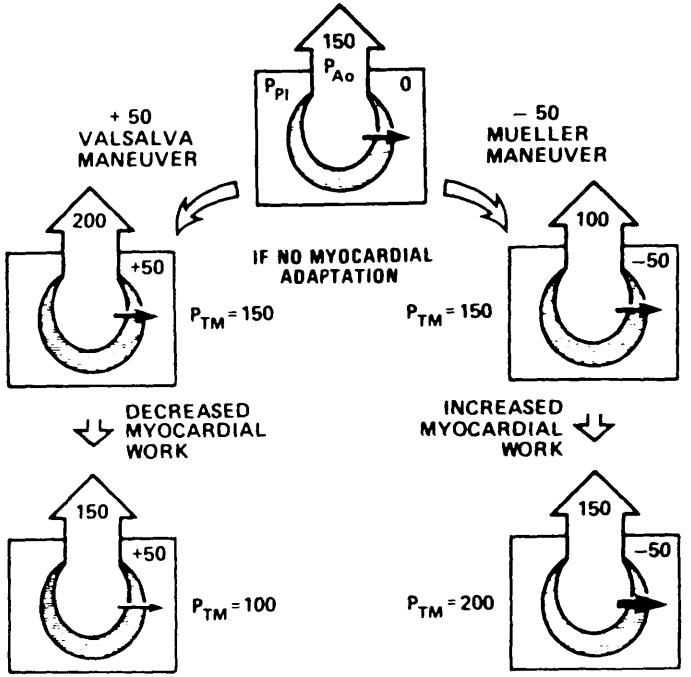



**Figure 3** Schematic representation of the left ventricular (LV) wall, thoracic cavity, and aorta showing that opposite changes in pleural pressure Ppl as induced by a Valsalva's maneuver (positive Ppl) and by Mueller's maneuver (negative Ppl) induce opposite effects on LV transmural pressure (Ptm). (From Ref. 80.)

modilution technique they used was based on a special software developed to obtain a thermal beat-by-beat analysis of the RV ejection fraction (82). In addition, pleural pressure was estimated using an esophageal balloon in order to assess RV transmural pressures. All patients exhibited cyclic changes of RV ejection fraction throughout the respiratory cycle: RVEF was minimal (18%) during inspiration and coincided with the minimum pulmonary pulse pressure; conversely, the RVEF was maximal (46%) during the second beat after the onset of expiration and coincided with the maximum pulmonary pulse pressure (Fig. 4).

*Inspiration.* These results suggest that RV function was impaired during inspiration in the studied COPD patients. The investigators also observed an inspiratory enlargement of the RV cavity at both end-diastole and end-systole on 2D echocardiography. It is well recognized that venous return to the RV is augmented during inspiration with a concurrent increase in RV stroke volume (78). The inspiratory increase in RV diastolic size is related to a phasic improve-

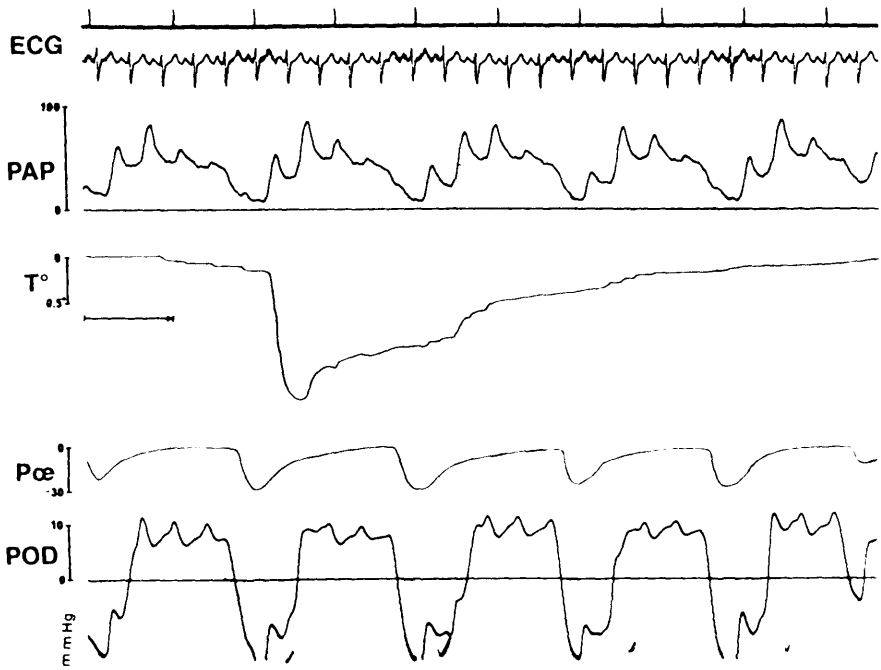



**Figure 4** Tracing of a simultaneous recording of ECG, pulmonary artery pressure (PAP), thermodilution curve (T°), esophageal pressure (Poe), and right atrial pressure (POD) from a COPD patient during acute exacerbation of the disease. A cold bolus was injected over the time marked by the arrow. (From Ref. 81.)

ment of venous return due to negative pleural pressure. In parallel, the initial part of the abdominal vena cava exhibited an inspiratory collapse, as already reported in asthma attack (83). This inspiratory collapse may be explained by the inability of collapsible vessels to transmit a negative pressure. The collapse of abdominal vena cava is expected to limit the effect of deep negative pleural pressure in promoting venous return and thus to have a protective effect against excessive enlargement of the RV cavity. However, despite elevated RV preload during inspiration, thermal RV ejection fraction, RV fractional area of contraction, and pulmonary pulse pressure were found to be low in this setting. Two explanations can be invoked for this apparent discrepancy. Experimentally, the relationship between pulmonary vascular resistance and lung volume is U-shaped, the lowest point representing the normal functional residual capacity. Therefore, in normal respiratory conditions, lung inflation is expected to have little effect on pulmonary vascular resistance. By contrast, in patients with COPD in whom functional

residual capacity is markedly high, any increase in lung volume by tidal breath would sharply increase pulmonary vascular resistance, which, in turn, raises RV afterload. Another possibility was raised by Jardin et al. (83) to explain the RV inspiratory failure observed in asthma. It involves the possible restriction of the systolic RV free wall inward motion by the highly negative inspiratory pleural pressure. This is not obviously applicable to patients with COPD for the following reasons: (1) the mechanical impediment of RV contraction by low extramural pressure-induced "cupping" of its free wall may be less effective in the case of COPD-related RV hypertrophy; (2) the values of pleural pressure are less negative in COPD than those observed in asthma attack; and (3) the extramural pressure for the RV and the main pulmonary arteries are not readily different and, consequently, the RV wall stress is not markedly increased by this phenomenon. Thus, the inspiratory fall in pleural pressure increases not only RV afterload, but also RV preload, boosting extrathoracic blood into the RV.

*Expiration.* At the onset of expiration, the decrease in lung volume unloads the overfilled RV, allowing a sudden increase in RV ejection fraction and pulmonary pulse pressure. However, as expiration continues, positive pleural pressure may cause both the venous return and RV preload to be reduced to such a degree as to decrease RV ejection fraction, as this has recently been described for the left ventricle.

Finally, in acute exacerbations of COPD, phasic changes in RV loading conditions may induce marked changes in RV ejection fraction over the respiratory cycle. This should be taken into account when evaluating RV ejection fraction over several beats, and the results provided by the thermodilution technique must be averaged throughout a respiratory cycle to minimize changes related to airway pressure-induced modulation of RV ejection fraction.

*Pulsus Paradoxus.* Another frequently observed clinical manifestation of heart-lung interaction during acute exacerbation of COPD is pulsus paradoxus. This is usually defined as an inspiratory decrease in systolic arterial pressure by more than 10 mmHg. This is due to a combination of decreased LV preload from ventricular interdependence and increased LV afterload (80,84).

### Expiratory Impairment of Venous Return During Exercise in Emphysema

In patients with severe emphysema, the peak expiratory pleural pressure is frequently positive during quiet breathing and highly positive during exercise. This could impede venous return and limit cardiovascular adjustments to exercise. Even et al. (85) studied three groups of patients: group I with diffuse emphysema and unilateral giant bullae compressing lung parenchyma and shifting the heart towards the contralateral side, group II with advanced panlobular emphysema, and group III with chronic bronchitis and/or centrolobular emphysema. All patients were markedly short of breath at exercise. Patients in group III were hypoxemic, hypercapnic, and polycythemic with cardiomegaly and pulmonary

hypertension, but exhibited normal cardiac output at rest and exercise. Despite the clinical severity of their disease, the patients of groups I and II had near normal $Pao_2$ and $Paco_2$ at rest, which became severely abnormal at exercise, they had neither polycythemia nor pulmonary hypertension, and their cardiac size was normal or frequently diminished and cardiac output was reduced at rest and severely impaired at exercise. By analogy with mechanical ventilation, venous return is reduced during expiration in severe emphysema as a consequence of the elevation of intrathoracic pressure and/or the displacement of the right atrium and thoracic vena cava by unventilated and uncompressible bullae. Venous return and ventricular filling are reestablished during inspiration. Thus, what could be termed expiratory emphysematous cardiac tamponade occurs, severely limiting the cardiac adaptation to exercise. Surgical removal of bullae (group I) or of highly distended and destroyed emphysematous parts of the lung (group II) completely normalizes the cardiac size and the cardiac output at rest and exercise, drastically improving dyspnea and the clinical condition of the patients despite the absence of significant changes in pulmonary function tests.

### Changes in RV Function During Mechanical Ventilation

In the ICU, initiation of mechanical ventilation in COPD patients with ARF is often associated with acute cardiovascular collapse. Several mechanisms contribute to this complication, including the use of sedative drugs with vasodilator properties, which reduce the intrinsic sympathetic tone, but heart-lung interaction is most likely a predominant one. Indeed, positive airway pressure decreases the pressure gradient driving systemic venous return, which is a major contributor to hypotension (80). Similarly, hyperinflation and its consequence, intrinsic positive end-expiratory pressure (auto-PEEP), are associated with hemodynamic compromise (86). Hyperinflation results from inadequate expiratory time relative to the volume to be exhaled and the mechanical characteristics of the respiratory system. It is very common in patients with COPD and can easily be exaggerated by mechanical ventilation. The auto-PEEP–induced increase in mean intrathoracic pressure and lung volume can impair venous return, falsely increase pulmonary artery occlusion pressure, mechanically compress the cardiac fossa, increase pulmonary vascular resistance, and decrease cardiac output, ultimately causing hypotension (Fig. 5). If auto-PEEP is unrecognized, these events may be misinterpreted as primary cardiac failure and therapy may be misdirected. Hyperinflation in asthmatic patients under mechanical ventilation is an important factor of morbidity (87), including hypotension. This is probably also the case in COPD patients (see next section).

Mechanical ventilatory variables must be adjusted carefully to provide an adequate expiratory time and inspiratory-expiratory ratio (86). Management of this ventilator-induced hypotension should involve interventions aimed at either a decrease in right atrial pressure (decrease intrathoracic pressure) or an increase in venous driving pressure (increase mean systemic pressure). In the first instance,

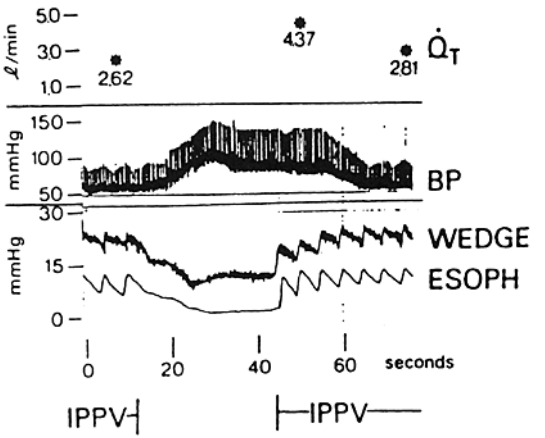



**Figure 5** The effect of temporary disconnection from mechanical ventilation (IPPV) in a patient with severe airway limitation and the auto-PEEP phenomenon. While on positive pressure ventilation, the combined hemodynamic profile of low cardiac output (QT = 2.62 L/min), hypotension, and elevated wedge pressure are suggestive of a primary cardiac dysfunction. However, following airway disconnection, cardiac output and arterial pressure rise and esophageal and wedge pressures fall. This suggests that increases in intrathoracic pressure and air trapping resulted in the hemodynamic embarrassment and incorrect estimates of wedge pressure determinations. Upon reinstituting IPPV, a similar decompensated cardiovascular pattern again resulted. (From Ref. 86.)

mean intrathoracic pressure can be reduced through ventilator manipulations such as decreasing inspiratory time by increasing inspiratory flow rates or decreasing tidal volume (88). The 1993 consensus conference on mechanical ventilation (89) has retained minimizing hyperinflation as an important objective of mechanical ventilation in COPD patients and proposed the use of high inspiratory flows, low minute ventilation, and low tidal volume to achieve it. It has also suggested that hypercapnia should be accepted if necessary for this purpose.

Also, if a given patient's status permits, a mode of mechanical ventilation associated with spontaneous breathing will result in lower mean intrathoracic pressure than when all breaths are machine-derived. Volume-cycled assist control should, however, be avoided in the initial management of the awake COPD patient (89).

Alternatively, mean systemic venous pressure can be increased by fluid replacement, leg elevation, or vasopressors.

### Inspiratory Impairment of LV Function During Weaning

In some COPD patients mechanically ventilated and difficult to wean from the ventilator, Lemaire et al. (90) demonstrated that the shift from a positive intra-

thoracic pressure regimen to the negative intrathoracic pressure regimen of unaided spontaneous breathing could be responsible for severe LV dysfunction leading to weaning failure. This was related both to ventricular interaction and increased LV afterload due to the large negative swings in pleural pressure. Details on this topic can be found in Chapter 15.

## III. Clinical Aspects of Heart-Lung Interactions in COPD

### A. Physical Examination

The symptoms and signs associated with pulmonary hypertension in patients with COPD are even more subtle and less specific than in other forms of pulmonary hypertension because of the underlying parenchymal lung disease. For example, increased exertional dyspnea may be the result of either airflow limitation or compromised oxygen transport because of impaired RV function. Similarly, neck vein distention and hepatomegaly may be indicative of RV dysfunction, or they may be the result of hyperinflation, with impaired venous return caused by increases in intrathoracic pressure and downward displacement of the liver, respectively (1). Symptoms may not be present until the resting pulmonary artery pressure is about two or more times normal. The symptoms most often associated with acute pulmonary hypertension include exertional dyspnea without orthopnea, fatigue, weakness, effort syncope, anginalike chest pain, palpitations, cough, hemoptysis and hoarseness; they may be present alone or in any combination (91).

The sensitivity and specificity of symptoms and signs associated with pulmonary vascular disease in COPD have not been previously examined. Salvaterra and Rubin (1) reported that, in their experience, there are, however, several signs and symptoms in the setting of COPD that are suggestive of the development of pulmonary vascular disease and that may warrant further evaluation. A progressive decrease in exercise tolerance in the absence of worsening airflow obstruction is helpful in suggesting a cardiovascular contribution. The palpation of a parasternal or subxiphoid RV lift, the auscultation of an accentuated pulmonary component to the second heart sound, or a right parasternal fourth heart sound are more robust signs of RV pressure overload. Late findings include a third heart sound or a murmur of tricuspid regurgitation, usually audible as a parasternal systolic murmur that increases in intensity with inspiration. Because these signs are usually indicative of severe pulmonary hypertension and RV dysfunction, they are not commonly seen in patients with COPD.

### B. Noninvasive Evaluation

#### *Pulmonary Function Tests and Blood Gases*

Lung function tests correlate poorly with the severity of pulmonary vascular disease. Conversely, arterial blood gases values, in particular $Pao_2$, are tightly

related to it. Patients with severe hypoxemia ($Pa_{O_2} \leq 55$ mmHg) will usually have the most significant degree of pulmonary hypertension (40). Pulmonary vascular disease can further contribute to hypoxemia by decreasing $Pv_{O_2}$, as a result of reduced cardiac output, or increased right-to-left shunting through a patent foramen ovale. The oramen ovale remains patent in 5% of the population and can be reopened by an elevated right atrial pressure (1).

### *Chest X-Ray*

The chest radiograph may provide useful clues to the presence of concomitant pulmonary hypertension. The most important radiographic signs of pulmonary hypertension are based on measurements of the diameter of the large pulmonary arteries. A commonly used measurement is the width of the descending branch of the right pulmonary artery. Its normal size ranges from 9 to 16 mm (91). Matthay et al. (92) showed that this diameter was greater than 20 mm in 19 of 20 patients with COPD and pulmonary hypertension. Moreover, they also found that an increased hilar thoracic index, defined as the ratio of the hilar width to the transverse diameter of the thorax, was 95% sensitive and 100% specific for pulmonary hypertension. Worsening pulmonary hypertension is also suggested by an increasing transverse diameter of the cardiac silhouette.

### *Electrocardiogram*

COPD patients with chronic pulmonary hypertension have ECG findings that reflect the consequences of the high pressures in the right side of the heart. However, the ECG abnormalities are usually less pronounced in COPD than in the other forms of pulmonary hypertension, probably because of the modest degree of pulmonary hypertension and because of the effects of hyperinflation. Right atrial hypertrophy is evidenced by a symmetrical and peaked P wave greater than 2.5 mm in amplitude in any lead. The classical ECG signs of RV hypertrophy are the following: qR observed in V1; the QRS axis in the frontal plan $\geq 110°$; delay of intrinsicoid deflection in V1 or V2 $\geq 0.035$ sec; R/S ratio in V1 $> 1$ or in V6 $< 1$. Butler et al. (1986) have assessed the diagnostic performance of three criteria for RV hypertrophy: (1) P wave $> 0.25$ mV in leads II, II, aVF, V1, or V2; (2) R wave amplitude $\leq 0.2$ mV in lead I; (3) A + R − PL $\geq 0.7$ mV (A = R or R′ in V1 or V2; R = S in I or V6; PL = S in V2). These three criteria achieved 89% sensitivity in a population with cor pulmonale–related RV hypertrophy (93).

### *Ultrasound*

Echocardiography represents a major advance in the field of noninvasive evaluation of RV function and heart-lung interactions. It allows one to look at RV size, the configuration of the interventricular septum, and contractility. It must, however, be noted that its usefulness is at times limited in COPD patients, due to

hyperinflation of the lungs and the marked respiratory variations in intrathoracic pressures. Signs of RV pressure overload and failure such as increased RV wall thickness, septal flattening or paradoxical motion, early closure of pulmonary valve, and incomplete closure of tricuspid valve are seldom recorded by standard 2D and M-mode echocardiography. Evaluation of peak PAP may be obtained with continuous wave doppler measurements of the tricuspid jet (94). The feasibility of this measurement in patients with COPD is low—24% (95)—but could be improved by using multiple view and contrast enhancement of the continuous wave doppler (96). The utility of transesophageal echocardiography has yet to be fully explored, but this technique has greater potential to provide satisfactory imaging of the right heart structures, albeit at the price of both cost and discomfort (1).

#### *Radionuclide Ventriculography*

Although PAP cannot be estimated with this technique, radionuclide ventriculography can provide useful information regarding RV function. An inverse relationship between PAP and RV ejection fraction has been observed in COPD with this technique. In most COPD patients with pulmonary hypertension, the RV ejection fraction is preserved at rest, but it does not increase appropriately during exercise (97).

#### *Magnetic Resonance Imaging*

MRI was utilized by Saito et al. (98), who reported that RV wall thickness and the ratio of RV wall thickness to LV posterior wall thickness correlated closely with PAP in 36 patients with COPD.

Noninvasive tests certainly provide valuable tools for evaluation of heart-lung interaction in COPD and are probably very useful to follow-up purposes. However, Weidemann and Matthay (54) recently claimed that hemodynamic monitoring cannot yet be replaced in the management of the acutely ill patient with RV failure, where it remains the mainstay. Right heart catheterization can confirm the elevated right atrial, RV, and pulmonary artery pressures. Although the influence of a concomitant tricuspid regurgitation on the estimation of thermal RV ejection fraction remains to be determined, thermodilution gives access to cardiac output and RV ejection fraction and volumes.

## IV. Therapeutic Implications

The management of chronic cor pulmonale resulting from COPD is multifaceted and includes treatment of promoting factors such as bronchoconstriction, respiratory tract infections, and retained secretions when they are present. It is not

uncommon to observe signs of cor pulmonale at the beginning of ARF and see them disappear during follow-up. Some studies have suggested that agents commonly used to treat airway obstruction such as terbutaline and aminophylline may also improve RV function, either by reducing RV afterload or increasing myocardial contractility (98a,99). However, these agents may have untoward effects such as tachycardia or arrhythmias. Accordingly, they should be used cautiously in patients with concomitant cardiovascular disease.

The following discussion focuses on therapies directed against the circulatory abnormalities of cor pulmonale, specifically, pulmonary hypertension and the resulting RV dysfunction.

### A. Therapy of Chronic Cor Pulmonale

#### *Oxygen Therapy*

*Short-term oxygen therapy* was evaluated by Degaute et al. (100). They studied 35 patients—hypoxemic ($Pa_{O_2} < 60$ mmHg) and hypercapnic ($Pa_{CO_2} > 44$ mmHg)—spontaneously breathing room air. Fifteen patients (group I) had severe hypoxemia ($Pa_{O_2}$ 40 ± 1 mmHg) and low oxygen delivery (493 ± 26 to 634 ± 26 $ml \cdot min^{-1} \cdot m^{-2}$). The other 20 (group II) were less hypoxemic ($Pa_{O_2}$ 49 ± 2 mmHg), with a higher oxygen delivery. In group I, 28% oxygen administration increased oxygen delivery (672 ± 37 $ml \cdot min^{-1} \cdot m^{-2}$), because arterial oxygen saturation improved, whereas cardiac output did not change. In group II, oxygen therapy failed to modify oxygen delivery because the rise in arterial oxygen saturation was offset by a reduction of cardiac output. This suggests that baseline oxygen delivery was inappropriately low in group I patients, who could not raise their cardiac output enough to maintain acceptable tissue oxygenation. It is of interest to note that short-term oxygen therapy did not reduce pulmonary hypertension in either group, possibly because of persistent hypercapnia and acidosis. Esteban et al. (101) recently reported similar results in a group of severely hypoxemic patients ($Pa_{O_2} < 45$ mmHg) during acute exacerbations of COPD. They found that oxygen therapy increased oxygen delivery without significant changes in pulmonary hypertension, cardiac output, or oxygen consumption. From these studies, it appears that hypoxic pulmonary vasoconstriction may not be the foremost mechanism of pulmonary hypertension in ARF of COPD.

The effects of one month continuous low-flow oxygen therapy on pulmonary hemodynamics have been assessed using both radionuclide ventriculography and invasive measurements in a small number of stable COPD patients (102). Changes in RV ejection fraction correlated with alterations in cardiac output and oxygen delivery, but not with alterations in pulmonary artery pressure and pulmonary vascular resistance, which remained minor. From these results, the investigators proposed that improved oxygen delivery in COPD under oxygen therapy primarily depends on RV output as a direct result of improved tissue (e.g.,

myocardial) oxygenation, rather than on decreased pulmonary vascular resistance. However, the impact of oxygen on hypoxic vasoconstriction may have been underestimated in this study because of a selection bias limiting analysis of the results in those patients with the highest pulmonary artery pressures. Finally, several studies provide evidence that RV dysfunction limits exercise performance in some COPD patients, in addition to the ventilatory limitation (44,103). Low-flow oxygen therapy can improve RV response to exercise in some patients, although maximum exercise capacity is generally not improved (104).

In two clinical trials sponsored by the U.S. National Institutes of Health (105) and the British Medical Research Council (BMRC) (47), *long-term oxygen therapy* clearly improved the survival of hypoxemic COPD patients ($Pao_2 < 60$ mmHg). The British study compared the effects of oxygen therapy (2 L/min) for about 15 hr/day including sleep time with no oxygen therapy. The U.S. study compared nocturnal oxygen therapy (12 hr/day) with so-called continuous oxygen therapy (at least 19 hr/day); the oxygen dose was chosen to raise $Pao_2$ to at least 65 mmHg and increased by 1 L/min at night. Although the two studies used similar entry criteria, the British patients had higher hematocrits, $Paco_2$, pulmonary artery pressures, and cardiac output (106).

Oxygen therapy proved beneficial in both studies. In the British study, the 5-year mortality in the untreated patients reached 67% vs. 45% in the oxygen-treated patients. In the U.S. study, mortalities in the group receiving nocturnal oxygen were 21 and 41% after 1 and 2 years, respectively, vs. 12 and 22% in the group receiving continuous oxygen therapy. In brief, "no oxygen is bad, oxygen for some of the time is better, but oxygen for most of the time is best" (107). The long-term oxygen therapy improvement in survival is associated with improvement of neuropsychological functions (106,108).

The mechanism underlying improved survival under long-term oxygen therapy is a matter of controversy. The hypothesis that cor pulmonale mortality is related to hypoxic pulmonary vasoconstriction as a source of pulmonary hypertension would lead one to expect that the oxygen therapy–associated reduction in mortality parallels at least a slowing progression of pulmonary hypertension. In the BMRC trial, PAP increased significantly in the group receiving no oxygen and remained stable in the treated group. In the NOTT study, pulmonary vascular resistance increased slightly in the nocturnal group and decreased slightly in the continuous oxygen group. Moreover, Weitzenblum et al. (109) reported significant decreases in mPAP (2.15 mmHg/yr) in 16 hypoxemic COPD patients receiving oxygen therapy (15–18 hr/day) for 1–6 years, whereas mPAP exhibited in the same patients a yearly increase of 1.47 mmHg. It seems, therefore, clear that oxygen therapy does slow down the progression of COPD-related pulmonary hypertension. Whether this is the hemodynamic improvement responsible for the beneficial effect on survival or if the two phenomena are unrelated remains to be established.

In the NOTT trial, only low pulmonary vascular resistance at entry was associated with better survival in the nocturnal oxygen group, and this was the case only for stroke volume in the continuous oxygen group (41). After 18 months, an average fall in hematocrit of 2.0% was observed in the nocturnal oxygen therapy patients and of 9.2% in the continuous oxygen therapy patients. Pulmonary vascular resistance also was affected by oxygen treatment: it increased by 6.5% on average in the nocturnal oxygen group vs. 11.1% in the continuous oxygen therapy group. Nevertheless, patients who had a low baseline vascular resistance showed improved survival from continuous oxygen therapy, and those with a high resistance did not. Combining the findings in the two treatment groups showed that large decreases in pulmonary vascular resistance tended to be associated with higher mortality than did small ones. These results suggested that although continuous oxygen therapy reduced pulmonary vascular resistance and mortality, the two effects were unrelated. However, a decrease in mPAP within the first 6 months of therapy was related to subsequent survival, after adjustment for the baseline mPAP (41). This decrease was associated with improvement in stroke volume. Ashutosh et al. (110) added further support to the hypothesis that oxygen-related hemodynamic changes are related to survival by finding that 85% of the responders to short-term oxygen therapy (decrease in mPAP $\geq$ 5 mmHg) were alive 2 years later vs. only 11% of the nonresponders.

Further work is required to identify precisely the subsets of COPD patients who benefit from oxygen therapy and those who do not. However, on the basis of the available studies, COPD patients should be started on continuous long-term oxygen therapy if the resting $Pao_2$ remains below 55 mmHg after a 3-week stabilization period on maximal medical therapy (111,112), if there is polycythemia, or if there is clinical evidence of pulmonary hypertension or cor pulmonale. The proposition that prolonged stabilization (113) or nocturnal oxygen therapy may achieve acceptable $Pao_2$ values (41) has been made. Such a strategy runs the risk of an inappropriate delay in initiating continuous oxygen therapy in some patients.

Up to now, evidence has been presented to support the concept that cardiac output may be important in the successful adaptation to COPD. There remains interest in pharmacological approaches to improve cardiac function in cor pulmonale.

### *Digitalis and Diuretics*

Although cardiotonic glucosides enhance the contractility of the RV myocardium, they also produce pulmonary vasoconstriction (114). Thus, the influence of digitalis upon RV performance is complex, and its use in cor pulmonale is associated with an increased frequency of cardiac arrhythmias in these hypoxemic patients (115). Moreover, Sylvester et al. (116) observed that, in dogs, digitalis increases the "unstressed reservoir volume" through an action on the peripheral vascula-

ture. This may adversely affect venous return and then cardiac output in COPD patients.

Finally, in patients with cor pulmonale, digitalis does not improve RV function at rest or during exercise, except in instances of coexisting left ventricular failure or a supraventricular tachyrhythmia (117). However, the possibility that digitalis may have favorable effects when used in combination with other medications cannot be excluded.

In contrast to the failing LV, the failing RV appears to be more dependent on preload, requiring a greater filling pressure to maintain cardiac output. The indication for diuretics is therefore less clear than it is in left heart failure. Diuretic-induced metabolic alkalosis is deleterious to gas exchanges and may be poorly tolerated by hypercapnic patients with COPD (1). When diuretics are used, careful monitoring of electrolytes is essential.

### *Theophylline and β-Adrenergic Agonists*

For several decades, theophylline has been widely used to treat COPD. In this setting, it has been shown to cause a modest subjective improvement of dyspnea scores and a slight objective improvement of bronchial obstruction, as well as a cardiovascular benefit with improved RV and LV ejection fractions (99,118). Others (119) showed the absence of effect on pulmonary vascular tone and on ventricular ejection fractions at rest and during exercise. Recently, Mols et al. (120) demonstrated a relationship between the blood level of aminophylline and variations of PAP and ventricular ejection fractions in nine stable COPD patients. Such a dose effect could explain the contradictory data reported in the literature.

Terbutaline, also frequently used as a bronchodilator in COPD, may provide similar beneficial cardiovascular effects unrelated to bronchodilatation and enhanced gas exchange (98). Such favorable hemodynamic changes followed oral administration of pirbuterol and persisted during 6 weeks of treatment (121).

### *Vasodilator Agents*

Success of systemic vasodilating agents in the management of left ventricular failure has stimulated much interest in the potential role of vasodilators in COPD-related pulmonary hypertension and cor pulmonale. Despite early enthusiasm, it is now clear that beneficial hemodynamic responses are observed in only a small portion of patients and are partially offset by deleterious effects on systemic hemodynamic and gas exchanges. These therapeutic agents are now regarded with a certain skepticism, but this has not precluded active investigation of the long-term use of vasodilators (54).

Most investigators used hydralazine, nitrates, or calcium channel blockers. Results with *hydralazine* are somewhat conflicting, some studies claiming benefi-

cial effects (58,98,122,123), and others indicating limited or detrimental effects (124,125). Dal Nogare and Rubin (123) showed that hydralazine lowered mean PAP and pulmonary vascular resistance during exercise and enhanced maximum cardiac output and mixed $P\bar{v}O_2$. However, they found no change in maximum oxygen consumption, probably because patients' efforts were limited by ventilatory factors. Some investigators have reported that hydralazine usually produces an increase in minute ventilation during rest and exercise. This phenomenon of rather obscure pathogenesis may account for an undesirable increase in dyspnea observed with hydralazine (126). The hemodynamic effects of hydralazine generally appear superior to those of nitroprusside and nitroglycerin, which essentially reduce RV preload, cardiac output, and $PaO_2$ (58,98). Flosequinan, a new orally active vasodilator with balanced venous and arterial actions, seems to favorably alter pulmonary hemodynamics relative to systemic hemodynamics and to result in a significant improvement in oxygen delivery (127).

*Nifedipine* as an inhibitor of pulmonary vasoconstriction (128) has received much attention (129–132). Some studies indicate that nifedipine often produces an acute fall in pulmonary vascular resistance while improving cardiac output and oxygen delivery (130–132). Exercise tolerance is, however, not improved, again perhaps because exercise is limited more by ventilatory factors than by cardiovascular dysfunction (132). Sturani et al. (129) demonstrated that acute hemodynamic effects of nifedipine were maintained after 2 months of therapy. Because of its deleterious influence on pulmonary ventilation-perfusion relationships (133), a decrease in $PaO_2$ is at times observed in some patients (130), but this reduction is usually mild. It is not constant (129,131). Recently, Mols et al. (134) showed that short-term administration of nifedipine improved the RV and LV systolic function by a fall in ventricular afterload and an increase in ventricular contractility. Improvement in ventricular compliance by a reflex sympathetic stimulation and an afterload reduction was also present. One should, however, be cautious not to extrapolate results of short-term, single-dose administration of nifedipine when reflex sympathetic stimulation would be maximal to long-term administration of this agent in COPD patients.

*Nitrendipine* is another calcium channel blocker with similar effects but long duration of action. Rubin and Moser (135) found that nitrendipine lowered pulmonary vascular resistance and increased cardiac output after 6 weeks of therapy. In addition, Michael et al. (136) found that nitrendipine attenuated the pulmonary vascular remodeling and RV hypertrophy caused by intermittent hypoxia in rats, suggesting a potential role for nitrendipine in the early treatment of COPD to prevent hypoxia-induced alterations of pulmonary circulation.

*Felodipine*, a new calcium antagonist with a prolonged duration of action and high vascular selectivity, reduced mean PAP and increased cardiac output without worsening gas exchange at rest and during exercise in 10 hypoxemic

patients with COPD during the 12 weeks of its administration (137). The incidence of side effects was relatively high in this study, which may constitute a significant impediment to large-scale clinical trials of this drug.

Limited data are available for the use of *captopril*, an inhibitor of the angiotensin-converting enzyme, in COPD patients. This vasodilator decreased mean PAP and increased cardiac output (138), but this could be followed by a pronounced systemic hypotension. The intravenous (139) and oral (140) administration of *prostaglandin* $E_1$ decreased mean PAP and increased cardiac output, but adverse effects were reported (hypotension, diarrhea, and flushing).

Andrivet et al. (141) recently reported that intravenous administration of *atrial natriuretic factor* (ANF) in COPD patients was associated with a dose-dependent decrease in PAP and a dose-dependent increase in blood flow perfusing poorly ventilated units. In spontaneously breathing patients, $Pao_2$ remained unchanged in spite of this worsening of ventilation-perfusion matching, presumably because of an increase in minute ventilation. This explanation was supported by the fact that in six patients mechanically ventilated—in other words, in whom ventilation was fixed—ANF infusion increased venous admixture and was associated with a slight dose-dependent decrease in $Pao_2$. Interestingly, the authors noted that the increased ventilation in their patients was not associated with dyspnea, conversely to what is observed for instance with hydralazine. The authors concluded that the balance between the hemodynamic effects of ANF and the minor decrease in $Pao_2$ seemed to them favorable and clinically relevant with respect to future therapeutic applications.

In conclusion, vasodilator therapy in COPD patients should be considered only when conventional therapy and oxygen have failed to improve signs of RV failure or pulmonary hypertension. Further studies evaluating the long-term effects of vasodilators are necessary to adequately define the indications in COPD patients. Another type of perspective is opened by the effects of nitric oxide on the ventilation-perfusion relationship. Indeed, recently, Adnot et al. (142) examined the responses to incremental infusion rates of acetylcholine or inhaled *nitric oxide* on hemodynamic and gas exchange in 13 patients with COPD. Pulmonary vascular resistance changes were similar in both interventions, but, by contrast to acetylcholine, nitric oxide inhalation induced selective pulmonary vasodilatation without systemic vasodilatation and improved gas exchange. Although sufficient data on the long-term toxicity of NO are not yet available, NO inhalation may potentially represent an alternative approach to treating some patients with severe COPD and pulmonary hypertension.

### *Phlebotomy*

Current evidence suggests that reduction of markedly elevated hematocrit values to less than 50% produces acute beneficial effects on hemodynamics, essentially

during exercise. Long-term benefits of repeated phlebotomy remain unclear. Oxygen therapy should reduce the number of COPD patients who become severely polycythemic. Consequently, phlebotomy should be reserved as adjunctive therapy in acute management of the markedly polycythemic COPD patient with cor pulmonale (54).

### B. Therapy of Acute Cor Pulmonale

Of course, the primary concern in the management of the COPD patient with acute RV failure is treatment of respiratory failure itself. Its specific therapies, including respiratory support, are not discussed in this chapter.

An important mechanism for maintaining cardiac output in COPD-related acute pulmonary hypertension is intravascular volume expansion, especially after initiation of mechanical ventilation that leads to a reduction of RV preload and an additional increase in RV afterload (82). Many intensivists believe that RV preload must be optimized as an initial step in managing acute RV failure. However, results obtained by Prewitt and Ghignone (143) in a dog model of acute pulmonary hypertension suggested that volume loading can be deleterious. Volume loading raising RV and LV end-diastolic pressures above 10 mmHg resulted in a decrease in cardiac output. This is probably due to the fact that increasing RV filling pressure in this setting will not increase stroke volume but will increase RV end-diastolic pressure and intrapericardial pressure, thus reversing the transseptal gradient. The hemodynamic situation is not quite similar in COPD patients during ARF because of the chronic hypertrophy and dilatation of the RV. Usually, oxygen therapy unloads the RV by decreasing pulmonary vascular resistance, and volume loading is not necessary, except for patients in whom blood pressure abruptly decreases upon initiation of mechanical ventilation.

Inotropic agents to increase RV contractility can be important tools. In an experimental model of acute pulmonary hypertension, norepinephrine and dobutamine enhanced RV function (143). In the clinical setting, they can be used but are not frequently needed, because the RV contractile reserve is normal or high. The need for inotropic support in COPD patients with ARF should raise the question of an additional cardiac dysfunction due to coronary artery disease, sepsis, or severe pulmonary embolism, for example.

The maintenance of aortic pressure is an important issue in managing such patients. When treating a patient with acute cor pulmonale, the clinician should be cautious in applying therapies that may decrease systemic blood pressure. Agents that increase aortic pressure have been shown to reverse RV ischemia and actually improve RV function in presence of hypotension induced by acute pulmonary hypertension (143). Norepinephrine and dopamine are the drugs of choice. A low blood pressure after adequate volume loading is rarely observed in COPD patients and should lead to a search for thromboembolic or septic complications.

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# 10

# Pulmonary Vascular Reactivity in Acute Respiratory Failure of Chronic Obstructive Pulmonary Disease

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## I. Introduction

Pulmonary hypertension during episodes of acute respiratory failure (ARF) of chronic obstructive pulmonary disease (COPD) has now been recognized for decades (1). It generally corresponds to a rise in a preexisting chronic pulmonary hypertension corresponding to the underlying COPD, which, remarkably, is usually mild to moderate. Indeed, mean pulmonary arterial pressure (PAP) seldom reaches 30 mmHg at rest in this condition, even in patients with chronic respiratory failure (2,3).

Pulmonary hypertension can substantially worsen during acute phases of the disease, where PAP may exceed 50 mmHg (4,5). Pulmonary artery occlusion pressure (PAOP) is sometimes found to be increased (4), but it is usually little affected (6). As a result, the driving pressure across the pulmonary circulation, namely, the difference between PAP and PAOP, increases markedly (6). A concomitant rise in cardiac index is possible (4) but often modest (6,7). The disproportionate increase in driving pressure with respect to cardiac output is responsible for a marked augmentation of calculated pulmonary vascular resistance (PVR), defined as the ratio of driving pressure to cardiac output.

That PVR, hence the degree of pulmonary hypertension, peaks during ARF

is consistently found by most investigators (4–7). However, the question as to how this pulmonary hypertensive crisis should be dealt with is still a matter of debate. Indeed, one can regard the increase in PVR either as a burden on the right ventricle or as a protective mechanism tending to reduce ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch.

## II. Influence of Pulmonary Hypertension on Right Ventricular Function

Heart-lung interactions during ARF of COPD are comprehensively reviewed in Chapter 9 of this volume. Hereafter will we only discuss whether elevated PVR adversely affects right ventricular function and, if so, to what extent reversing the rising pressure by use of oxygen or pharmacological agents is or not beneficial.

Clinical signs of cor pulmonale or pulmonary heart disease (8) are usually associated with poor prognosis and high mortality in COPD (9). Classical concepts are as follows: as the pulmonary circulation works in series with the right ventricle, changes in pulmonary hemodynamics are thought to necessarily affect right ventricular afterload. As a consequence, the chronically elevated pulmonary arterial pressure, overloading the right ventricle, leads to right ventricular hypertrophy. Enlargement of the right ventricle at this stage represents an adaptive mechanism for it to cope with the augmented load. As the disease progresses, the overwhelmed right ventricle may fail to adequately respond to the increased hemodynamic burden, which defines right heart failure. Because increased PAP and clinical signs usually attributed to right heart failure are often concomitant in ARF of COPD, and because the latter usually recede with the return of the former to its baseline values, it is commonplace to believe that episodes of right heart failure are particularly prone to occur during acute exacerbations of respiratory failure. However, this link does not seem to be as tight as initially thought (10,11). Indeed, it can be misleading to consider as "failure" a situation in which the right ventricle facing increased afterload is able to increase its output, and the term "right ventricular dysfunction" is probably more realistic from a pathophysiological point of view. In the following paragraphs we will review the current evidence challenging the classical belief that pulmonary hypertension seriously compromises right ventricular function in COPD.

Two preliminary remarks should first be made. On the one hand, equating events that involve the systemic circulation and the left ventricle with events happening in the pulmonary circulation and the right ventricle can be misleading, and the behavior of the right ventricle may not parallel that of the left ventricle in the face of raised arterial pressure. In COPD, pulmonary hypertension is generally mild (2,3) and even during ARF seldom reaches levels such as those encountered in primary pulmonary hypertension (12) or repeated or massive pulmonary embo-

lism (13). With this in mind, the degree of hemodynamic load that the right ventricle has to bear in ARF of COPD remains low compared to what it can be for the left ventricle in the presence of systemic hypertension. Acute right heart failure is much less likely to occur in COPD than in pulmonary embolic disease. Furthermore, progression of pulmonary hypertension in COPD is generally slow (14), and there is enough time for efficient adaptative mechanisms to take place. Several studies of large groups of patients by repeated right heart catheterization have found little change in pulmonary hemodynamics over periods ranging from 18 to 166 months, with an average increase in PAP of around 0.5 mmHg per year and per patient (15–18). Over time, changes in the configuration and mass of the right ventricle probably allow better "tolerance" of acute impairments.

On the other hand, equating right ventricular afterload with measurements of PVR and PAP can also be misleading. By definition, right ventricular afterload is the result of the stress or tension acting on the ventricular wall immediately after the onset of its shortening, and it should be measured as a force per unit of cross-sectional area acting on the right ventricular wall (19). Accurate assessment of the right ventricular stress requires measurements of both the right ventricular volume and its wall thickness. Given the complex geometry of the right ventricle, these measurements are often fraught with difficulties. Therefore, right ventricular afterload is generally assimilated to PAP and PVR, the latter being considered slightly more accurate an estimate. It should be kept in mind that both indexes are at best an approximation of what the right ventricle afterload actually is.

With these two points in mind, one may question whether increased PAP or PVR could at all account for the development of right ventricular "failure" in COPD, including during acute exacerbations.

Peripheral edema, a common symptom of cor pulmonale, might be viewed as the reflect of the failure of the right heart pump to cope with systemic venous return. MacNee et al. (20) have specifically addressed this question and investigated the effect of raised PAP on right ventricular function. These authors studied a group of 14 patients, 6 of whom had ARF presenting with gross peripheral edema, whereas the remaining 8 patients were clinically stable and did not have edema. On average, right ventricular ejection fraction (RVEF) was lower in patients with edema as compared with those without edema. However, the impaired RVEF could not be explained by the severity of pulmonary hypertension, as the levels of PAP were similar in all patients. This clearly illustrates that afterload of the right ventricle is far from being completely described by PAP. Moreover, RVEF is not only determined by afterload, and the pathogenesis of edema observed in ARF or COPD cannot be completely related to right heart failure (21).

All in all, current knowledge indicates that the link between raised PAP and right heart failure in ARF of COPD is a weak one. This does not mean that right ventricular function is normal in this setting, and it would also be incorrect to deny the fact that severe, refractory right ventricular failure can be present in some

cases, especially in patients with end-stage COPD. Reducing right ventricular afterload in those instances should improve right ventricular function. The question, however, is still open as to whether reducing the raised pressure and resistance to blood flow in the pulmonary vascular bed using pharmacological means might be of benefit for patients, especially when other factors such as arterial oxygenation and systemic effects of the drugs are taken into account. These points will be reviewed in the following sections.

## III. Use of Pulmonary Vasodilators in Acute Exacerbations of COPD

The rationale for using vasodilators is based on the contention that pulmonary vasoconstriction is an important component of pulmonary hypertension. The ideal response to a vasodilator is a reduction of PAP with a rise in cardiac output (22). As a result, a vasodilator can be considered effective if there is a fall in both PAP and PVR (23).

As discussed above, that PVR and PAP further rise during acute exacerbations of COPD is unquestionable. However, the increase in resistance and pressure that occurs in the pulmonary vascular bed is most often transient, and pulmonary hemodynamics return to baseline values when the patients are back to their steady clinical state. Therefore, the only rationale for treating acute worsening of pulmonary hypertension in COPD would be to prevent dramatic increases in right ventricular afterload that could precipitate failure of the right pump. Theoretically such a possibility exists, especially when the combination of hypercapnia, acidosis, and hypoxemia promotes excessive pulmonary vasoconstriction.

Dilatation of a preconstricted vascular bed can be obtained by oxygen administration or pharmacological agents. In the last part of this chapter, we will examine the effects of acute administration of either oxygen or vasodilators on pulmonary hemodynamics and arterial oxygenation during ARF of COPD. Long-term oxygen or vasodilator therapy in patients with stable COPD will not be discussed. Recent extensive reviews can be found elsewhere (11,24,25).

### A. Pulmonary Hemodynamic Effects of Acute Oxygen Administration

Oxygen therapy in ARF of COPD aims at improving tissue oxygenation. It is specifically discussed in Chapter 22 of this volume.

From the hemodynamic point of view, response to oxygen therapy in COPD patients during ARF is usually characterized by a decrease in cardiac output and an increase in oxygen delivery as a result of increased arterial oxygen content. The ratio of oxygen delivery to oxygen consumption defines a "coefficient of oxygen delivery" (26). Expressing the response of COPD patients with ARF in terms of

this coefficient allows one to individualize two groups of patients. In the first, oxygen therapy is associated to a significant increase in oxygen delivery (27) without change in cardiac output (7,27). These patients are the most severely hypoxemic ones. The other group is characterized by a poorer response to oxygen, with a decreased cardiac output but no change in oxygen delivery. The patients in this group are those who present with less severe hypoxemia (27) and are probably less likely to benefit from oxygen therapy.

Hypoxic pulmonary vasoconstriction is generally considered the main underlying mechanism of increased pulmonary vascular tone in ARF of COPD. If this holds true, one would expect oxygen therapy to alleviate pulmonary hypertension by suppressing the hypoxic stimulus. This is indeed the case in most patients, in whom breathing oxygen significantly reduces PAP and PVR (7,20). However, pulmonary vasodilatation in response to oxygen does not seem to occur in a subset of patients having similar levels of pulmonary hypertension and hypoxemia (27,28). Moreover, breathing oxygen does not significantly modify pulmonary hemodynamics in those patients presenting with the most profound levels of hypoxemia [i.e., partial pressure of arterial oxygen ($Pa_{O_2}$) below 40 mmHg (29)]. This imperfect link between the vasodilatory effects of oxygen therapy and the severity of hypoxemia has led some investigators to suggest a role for mechanisms other than alveolar hypoxia to account for the increased pulmonary vascular tone in decompensated COPD. Hypercapnia and the resulting acidosis are the likely other candidates (30).

### B. Vasodilator Therapy

#### *Systemic Vasodilators*

The use of vasodilators other than oxygen in the treatment of COPD (in stable state or during ARF) is often fraught with difficulties (31). Indeed, while it has long been a temptation to use potent systemic vasodilators to reduce COPD-related pulmonary hypertension, the beneficial effects of such a therapeutic approach remain questionable. As a matter of fact, vasodilators in this setting have unwanted effects.

First, as expected from their intrinsic properties, systemic vasodilators do produce systemic hypotension. This remains true even when they are directly infused into the pulmonary circulation. It is therefore not surprising that the fall in pulmonary vascular resistance provoked by systemic vasodilators has consistently been associated with a concomitant fall in systemic vascular resistance. This has been observed with all systemic vasodilatory agents tried so far in ARF of COPD, including acetylcholine (7), the calcium channel blocker nifedipine (32), prostaglandin $E_1$ (33), and the nitrovasodilator nitroglycerin (34). Similarly, systemic hypotension occurs during the course of pharmacologically-induced pulmonary vasodilatation with an array of nonspecific vasodilators in patients with stable

COPD (reviewed in Refs. 11,24,25). Not only could occurrence of systemic hypotension limit the beneficial effects of the drugs, but it also might, if exaggerated, become fatal in some cases. In patients with primary pulmonary hypertension and right ventricular failure, a profound drop in coronary pressure gradient resulting from excessive systemic hypotension has been reported to cause sinoatrial ischemia, with fatal issue in some cases (35).

Second, it has been demonstrated that systemic vasodilators in COPD almost unavoidably deteriorate gas exchanges. Halmagyi and Coates were among the first to consider $\dot{V}_A/\dot{Q}$ mismatching as a possible explanation for the worsened hypoxemia in patients receiving intravenous aminophylline (36). Systemic vasodilators act on pulmonary vasculature as a whole and induce vasodilatation in well-ventilated lung units as well as poorly ventilated ones. In other words, part of total pulmonary blood flow is diverted from normal or high $\dot{V}_A/\dot{Q}$ regions to hypoventilated regions. This can be viewed as the result of blunting a "protective" hypoxic pulmonary vasoconstriction. This inappropriate pulmonary vasodilatation in poorly ventilated lung units therefore results in reduced arterial oxygenation. Such a deleterious mechanism has been documented with the calcium channel blocker nifedipine (37) and with practically all other classes of vasodilators (reviewed in Ref. 38).

### *Inhaled Nitric Oxide*

From the above considerations, it appears that a vasodilator acceptable for use in COPD patients should have detrimental effects on neither the systemic circulation nor pulmonary gas exchanges. The quest for such a selective pulmonary vasodilator has been a difficult task, even though purine nucleosides such as adenosine, which are rapidly metabolized by the lungs, may be considered somehow selective pulmonary vasodilators (39). However, the best molecule so far available to induce selective pulmonary vasodilatation in patients with pulmonary hypertension is a two-atom oxygen-derived free radical gas—nitric oxide (NO).

More than a decade ago, the existence of an extremely labile and potent endogenous vasodilator synthesized by the endothelium, termed endothelium-derived relaxing factor (EDRF), was established by Furchgott and Zawadzki (40). The nature of EDRF since remained elusive, until experimental results from several laboratories identified it as the free radical NO (41,42). The molecular target of NO is the soluble enzyme guanylate cyclase (43), stimulation of which by NO increases the level of the second messenger cyclic guanosine monophosphate within vascular smooth muscle, thereby causing vasorelaxation (44). The nitrogen atom of NO is derived from the N-guanidino terminal of the amino acid, L-arginine, whereas the oxygen atom is provided by molecular oxygen (43). NO is synthesized from these two precursors by a newly discovered family of enzymes, the NO synthases (NOSs). The complementary DNA for various isoforms of the

NOS family have been recently cloned and their amino acid primary structures sequenced (45). There are two major subgroups of NOS isoforms: constitutive and inducible. Endothelial NOSs are predominantly constitutive and most certainly play a key role in the modulation of systemic (46) and pulmonary (47) vascular tone. One of the inducible NOS isoforms probably mediates the cytotoxic activity of activated macrophages against numerous pathogens and intracellular microorganisms (48). Another inducible NOS isoform, which accounts for pathological synthesis of large amounts of NO, is thought to be the major cause of the refractory hypotension seen in human septic shock (49). The activity of these different NOS isoforms is highly regulated, requiring the presence of specific cofactors, including the calcium/calmodulin complex and reduced nicotinamide adenine dinucleotide phosphate (43). The synthesis of NO is stereospecifically inhibited by various L-arginine analogs, which act as competitive inhibitors of both the constitutive and inducible NOS isoforms (43). No specific inhibitor of the inducible NOS is as yet available.

As in other mammalian species, pulmonary endothelium-dependent relaxation mediated by NO is also present in humans (50). In vivo studies suggest that endogenous NO may have physiological importance in the modulation of human pulmonary circulation (47). Indeed, endogenous NO is present in the exhaled air from spontaneously breathing healthy subjects (51,52). Furthermore, significant increases in NO output are observed in conditions that might alter pulmonary and bronchial vasoreactivity, such as exertion and hypoxia (52). Data from studies using isolated vascular rings or perfused lungs also strongly suggest that endothelium-derived NO modulates pulmonary vasoreactivity in normoxia (53) and during acute alveolar hypoxia (54). Although some controversies still exist as to its rate of production during chronic hypoxia (55,56), endogenous NO probably has a pivotal role in the modulation of pulmonary vascular tone in health and pulmonary vascular disease (47,57). Indeed, most authors agree that NO is probably the major paracrine mediator that can rapidly adapt its rate of synthesis and/or release in response to acute increases in pulmonary vascular tone. Hence, a possible physiological role for NO would be to protect the pulmonary vasculature against disproportionate vasoconstriction that might result from various chemical and physical stimuli (47,57).

Knowing that NO is rapidly inactivated by hemoglobin (58), it has been hypothesized that NO, given by inhalation, could be such a selective pulmonary vasodilator (59). After entering the airways, inhaled NO primarily reaches the pulmonary vascular smooth muscle through diffusion from alveolar spaces, thereby causing pulmonary vasodilatation (Fig. 1). Once it reaches the luminal site of pulmonary endothelial cells, NO is rapidly bound to circulating hemoglobin and therefore inactivated (Fig. 1). Thus, no downstream vasodilatory effect is likely to occur. The recent suggestion that NO could be carried away by serum albumin, which subsequently releases NO downstream, makes systemic hypoten-

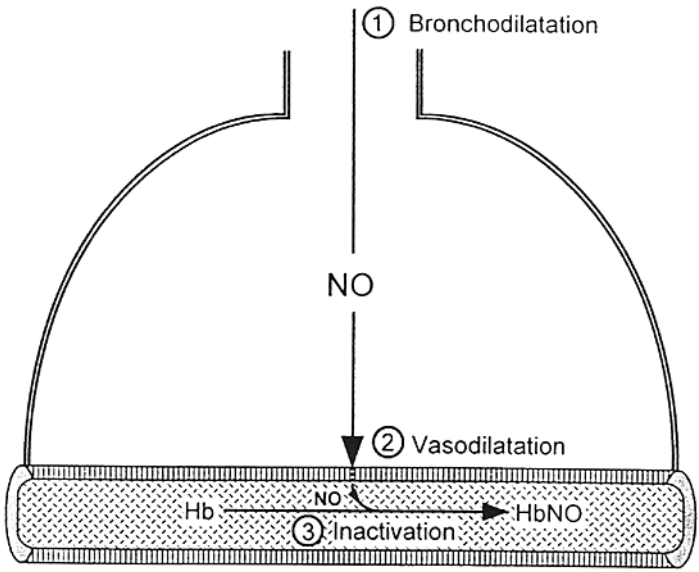


**Figure 1** Sites of action of inhaled NO. When given by inhalation, NO first dilates the respiratory tract (1), then relaxes the pulmonary vasculature (2). NO diffusing from alveolar spaces to the blood stream is rapidly bound to hemoglobin (Hb). The resulting HbNO is devoid of vasodilating effects (3), hence the absence of systemic hypotension.

sion a theoretical possibility (60). However, to the best of our knowledge, such an effect has not been reported in humans. Inhaled NO has been successfully applied in animals to reverse hypoxic and thromboxane-induced pulmonary vasoconstriction (61). In humans, the short-term inhalation of NO also produces significant and selective pulmonary vasodilatory effects in newborn infants with persistent pulmonary hypertension (62,63) and in adults with primary pulmonary hypertension (64) or acute respiratory distress syndrome (ARDS) (65,66). Inhaled NO has also been successfully administered to patients with stable COPD and mild pulmonary hypertension (67). In this setting again, inhaled NO has proved to be a potent and selective pulmonary vasodilator, unlike infused acetylcholine, which also decreases systemic vascular resistance (67). In mechanically ventilated patients presenting with acute decompensation of COPD, inhaled NO produces the same selective and potent vasodilatory effect on the pulmonary circulation (68). Furthermore, when given by inhalation, NO has a unique ability to improve gas exchange, hence arterial oxygenation, in both adults with ARDS (65,66) and newborn babies with refractory hypoxemia (62,63,69), as well as in patients with COPD (67). Thus, unlike infused systemic vasodilators (e.g., prostacyclin and acetyl-

choline), which dilate pulmonary vessels of ventilated as well as nonventilated lung units (Fig. 2A), inhaled NO preferentially induces vasodilatation in the former (Fig. 2B). As a result, $\dot{V}_A/\dot{Q}$ mismatching is reduced as shown by a decrease in intrapulmonary shunting ($\dot{Q}s/\dot{Q}T$), and gas exchange is improved as shown by an increase in $Pa_{O_2}$ (Fig. 2B). Such beneficial effects of inhaled NO have been convincingly further documented in a recent study using echocardiography in newborn infants with severe hypoxemia (69). In these babies, it has been found that inhaled NO exerts its beneficial effects by decreasing pulmonary vascular resistance as much as by improving $\dot{V}_A/\dot{Q}$ matching (69).

An elegant way to improve arterial oxygenation is to combine the use of inhaled NO with infused almitrine (70). Among other complex effects, almitrine reinforces hypoxic pulmonary vasoconstriction. This participates to its beneficial effects on $\dot{V}_A/\dot{Q}$ matching in COPD (71). Almitrine-related pulmonary vasoconstriction predominates in the shunting vascular bed, therefore reducing $\dot{Q}s/\dot{Q}T$ and improving arterial oxygenation (Fig. 2C).

It is possible that the inhaled route of administration, as much as NO itself, is instrumental in obtaining such beneficial effects on arterial oxygenation. This is in line with improvements of similar magnitude that have been observed with aerosolized prostacyclin in ARDS (72). Together with the marked increase in arterial oxygenation, a slight but significant decrease in partial pressure of arterial carbon dioxide ($Pa_{CO_2}$) is seen with inhaled NO in patients with ARDS (66) and ARF of COPD (68). It is likely that the bronchodilatory effects of NO (73) may account for this decrease in $Pa_{CO_2}$ by opening up parts of the lungs that were previously poorly ventilated. This contention has been recently supported by the

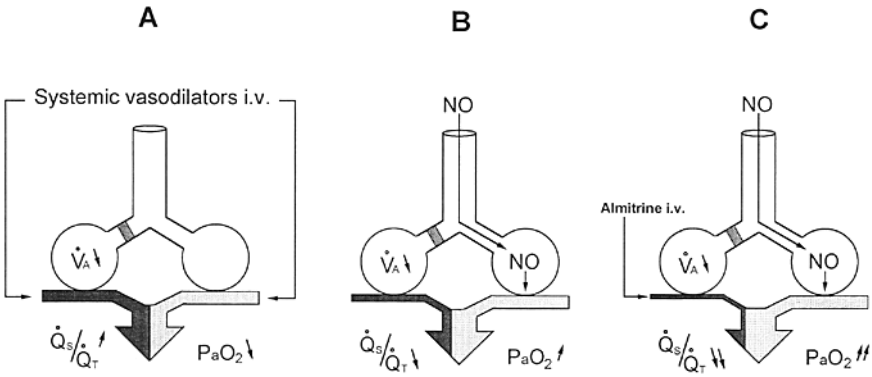


**Figure 2** Effects of (A) infused systemic vasodilators, (B) inhaled NO, and (C) the combination of inhaled NO with a pulmonary vasoconstrictor (e.g., almitrine) on intrapulmonary shunting $\dot{Q}s/\dot{Q}T$ and partial pressure of arterial oxygen ($Pa_{O_2}$).

demonstration that in patients with stable COPD, alveolar ventilation may increase with inhaled NO in some occasions (74). Inhaled NO also improves right ventricular function in patients with ARDS (66) and ARF of COPD (68). This result is, however, hardly a surprise, given the ability of inhaled NO to reduce right ventricular afterload in patients with severe pulmonary hypertension.

To date, three main difficulties remain and need to be addressed as to the use of inhaled NO in clinical settings. Firstly, to take the example of ARDS, it is now apparent that despite initial optimistic reports (65), not all patients are likely to benefit from inhaled NO, even with doses higher than 40 ppm (75). Second, weaning patients who are treated with long-term inhaled NO may be fraught with difficulties, as exogenous NO could switch off its endogenous production (76). Finally, potential harmful effects of this oxygen-derived free radical remain to be defined. Under physiological conditions, there are at least three redox forms of NO, which, either by gaining or loosing an electron, are converted to nitroxyl anion ($NO^-$) or nitrosonium ($NO^+$), respectively (77). A better understanding of the biochemistry of nitrogen oxides ($NO_X$), which include NO, is mandatory in order to predict, and therefore avoid, the toxicity induced by these molecules. Indeed, experimental data suggest that both endogenous and exogenous $NO_X$ react readily with oxygen, superoxide, water, nucleotides, metalloproteins, thiols, amines, and lipids (77). Biochemical end-products of these reactions may account for an array of toxic effects, including impaired mitochondrial respiration, lipid peroxidation, and mutagenesis (77). In the meantime, the most practical way of reducing NO toxicity is reducing the concentration of NO administered to patients. In this perspective, a recent study is encouraging in reporting significant beneficial effects of NO on gas exchange with doses ranging from 60 to 230 parts per billion (78), i.e., several hundred times less than doses that were initially recommended.

In conclusion, inhaled NO undoubtedly has made a recent, and dramatic, breakthrough in the way in which patients with pulmonary hypertension, either primary or secondary to COPD, are managed (79). This seems true when considering its specific and beneficial effects on pulmonary hemodynamics and gas exchange. However, as with other therapeutic advances, inhaled NO still needs to undergo large, multicenter, and controlled trials before we can determine whether the future management of these patients will rely on the use of a gas that was until recently regarded by many as merely an atmosphere pollutant (80).

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# 11

# Viral Infection as a Precipitating Factor

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## I. Introduction

The surface of the upper airways and oropharynx are permanently infected with a large number of organisms that make up the natural flora at these sites. Health is maintained as long as this symbiotic relationship exists, and disease is the result of addition of organisms capable of invading the host tissue barriers. The lower respiratory tract is sterile in health and usually becomes infected by contamination from the sites above the larynx. The viral infections that occur in the upper respiratory tract of humans several times each year may or may not be followed by a lower respiratory tract infection. In one careful study of 150 patients with COPD carried out over several years, viral and mycoplasma infections were present in 18% of 1030 episodes of acute respiratory illness (1). However, as 6% of the same patients carried these organisms in their respiratory tracts when they were free from acute respiratory disease, there was a statistically significant relationship between the acute episodes and the presence of virus in only some cases (Table 1). This suggests that the common respiratory viruses are capable of both living symbiotically with their host and of producing acute respiratory disease. The purpose of this chapter is to review the subject of viral infections as a precipitating factor in the development of acute respiratory failure in patients with

**Table 1** Association of Specific Infectious Agents with Acute Respiratory Illnesses*

| Type of infection | No. of infections | Associated with illness | Not associated with illness | Significance of association with illness |
|---|---|---|---|---|
| Rhinovirus | 56 | 49 | 7 | $p < 0.001$ |
| Influenza viruses | 53 | 50 | 3 | $p < 0.001$ |
| Parainfluenza viruses | 39 | 29 | 10 | $p < 0.001$ |
| Coronaviruses | 27 | 17 | 10 | $p < 0.05$ |
| Herpes simplex virus | 57 | 21 | 36 | NS |
| Respiratory syncytial virus | 16 | 8 | 8 | NS |
| Adenovirus | 14 | 7 | 7 | NS |
| Total | 262 | 181 | 81 | |

*From Ref. 1.

COPD. However, as methods for studying viruses are being increasingly refined, new information is accumulating rapidly, and our primary goal is to provide a framework into which this new information can be integrated.

## II. The Nature of Viruses

Viruses were discovered because their extremely small size allowed them to pass through bacteria-retaining filters. The subsequent introduction of cell culture techniques, electron microscopy, and the rapid development of immunohistochemical and molecular biological methods have greatly advanced the study of these fascinating organisms. Viruses are responsible for respiratory diseases ranging from conditions that are self-limiting, such as the common cold, to those in which there is rapid progression with massive lung destruction and death due to respiratory failure. Acute disease is produced by rapid proliferation of the virus with lysis of infected cells. On the other hand, there is growing evidence that chronic disease may result from either low-level proliferation of the complete virus (persistent infection) or the production of incomplete viral particles by partial expression of the viral genome (latent infection).

Viruses range in size from 20 to 300 nm and thus overlap with the small prokaryotic cells such as chlamydia and mycoplasma. On average, a virus is about 1/1000 the volume of a bacterium, and, with the exception of the larger poxviruses, they are only visible with the electron microscope. Individual viruses contain only one type of nucleic acid and can be readily classified on the basis of the type of nucleic acid that forms their genome. Because they lack a protein-synthesizing apparatus and energy-producing systems, viruses are obligate intracellular parasites. In an extracellular environment, a virus exists as a purely chemi-

cal entity that is incapable of replication or any of the other activities associated with living organisms. Many viruses contain only protein and nucleic acid, and although some have a lipid outer membrane, none contains free polysaccharides.

The process by which a virus infects a host cell is outlined in Figure 1. The virus must first adhere to the cell surface, penetrate the cell membrane, and uncoat its nucleic acid. The earliest viral proteins produced are the polymerases and transcription factors essential for the replication of the viral nucleic acid. The structural proteins are expressed subsequently, the complete virus is assembled from the nucleic acid, and structural proteins and assembled viruses are then either shed from the surface of the cell or released in large numbers by cell lysis to infect other cells. The possible outcomes of acute viral infection include resolution in which there is complete elimination of the virus from the host, fulminant infection causing death of the host, persistent infection characterized by low-level replication of the complete virus, or latent infection where viral DNA remains within the host cell and can express proteins without assembly of a complete virus.

The principal method of identifying replication of a virus is by viral culture. Individual viruses can then be further identified by either the nature of the effects

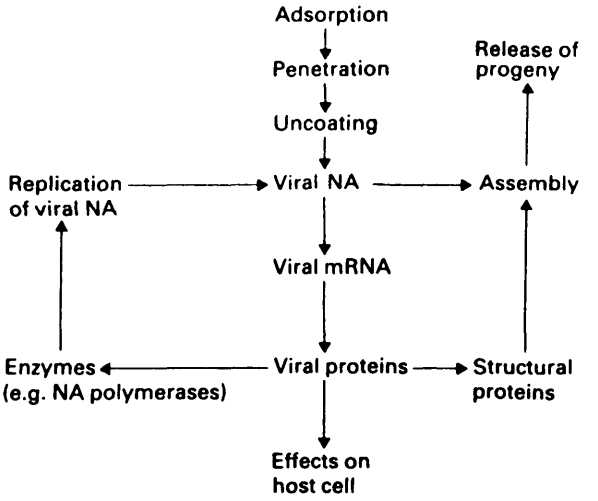



**Figure 1** Steps in the infection of a host cell by a virus include adsorption onto the cell surface, penetration through the cell membrane, uncoating of the viral nucleic acid, and the generation of mRNA transcripts from the early genes. These early genes include those for the nucleic acid polymerases required to replicate the viral DNA and those required to generate structural proteins. The complete virus is then assembled and released either by lysis of the cell or shedding from the surface of an intact cell. Viral DNA can also integrate into the host genome and produce important proteins without replication of the complete virus. (From Ref. 8.)

they have on the cultured cells (cytopathic effect) and identification of viral proteins by immunocytochemistry or their structure revealed by electron microscopy. Viral nucleic acid can be detected at very low levels using highly sensitive PCR techniques and specifically identified by hybridization to isotopic or non-isotopic probes. Increasingly, these procedures are being applied to infected tissue obtained from biopsies and autopsies, and the information obtained using this technology is providing a much better understanding of the molecular mechanisms of viral infection.

## III. Viral Infection of the Lower Respiratory Tract

Late in the last century, Holt (2) described a condition in children, which he referred to as acute catarrhal bronchitis, and divided it into a mild form that involved larger airways and a more severe form, which he called capillary bronchitis. He recognized that the pathological process was an acute inflammation of the airway wall and described the swelling, desquamation of the epithelium, and exudation of purulent mucus into the smaller airways. He also reported that the lungs from these patients were more often inflated than collapsed at autopsy, there was enlargement of hilar lymph nodes, and, in contrast to bronchopneumonia, there was considerably less exudate in the airspace. The more recent development of immunofluorescent techniques and the bedside inoculation of secretions into susceptible cell lines have now shown that these infections can be initiated by respiratory syncytial virus (RSV) (3), adenovirus (4), parainfluenza virus (5), rhinovirus (6), and influenza virus (7). When these infections extend into the lower respiratory tract, they can produce bronchitis, bronchiolitis, pneumonia, or some combination of disease at these three sites. In adult patients with COPD, these infections are superimposed on the inflammatory process already present in the lower respiratory tract. Smith et al. (1) used strict clinical criteria to identify upper and lower respiratory tract infections and viral culture and analysis of acute and convalescent serum to identify viral infections in a large group of patients with COPD. Their results (Table 1) showed that acute respiratory illness was statistically significantly associated with rhinovirus, influenza, parainfluenza, and coronavirus infection, but these viruses could also be present in some patients when they did not have an acute respiratory illness. Although herpes simplex, RSV, and adenovirus were also found in the respiratory tract of these patients, their presence was not related to acute respiratory illness in a statistically significant way.

## IV. Classification of Viral Infections

Figure 2 shows a classification of viruses based on the nature of the nucleic acid in their genome. The messenger RNA mRNA used to generate viral nucleic acid and

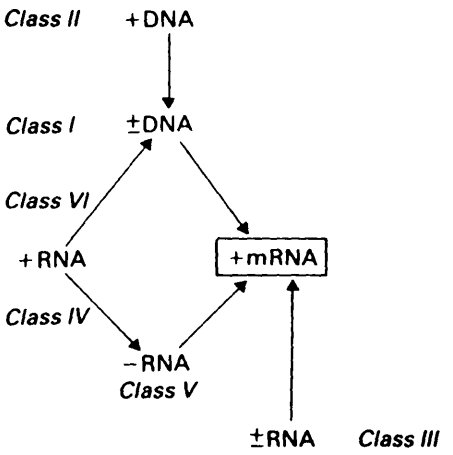



**Figure 2** A classification of viruses based on their nucleic acid. mRNA required for replication of either the viral genome or its structural proteins is designated + and double-stranded nucleic acids are designated as ±. Class I viruses (double-stranded DNA viruses) include adenovirus and the herpesviruses, which are important causes of lung disease. The Class V, single-stranded (−) RNA viruses include influenza, parainfluenza, and RSV and are also important causes of respiratory disease. Class IV viruses are single-stranded (+) RNA viruses, such as rhinovirus and coronaviruses, and produce a great deal of respiratory misery, but the majority of this is limited to the upper respiratory tract. Class VI viruses such as HIV require reverse transcriptase to produce complementary DNA, which can serve as a template for production of new viral genome or be integrated into the host genome. (From Ref. 8.)

protein is designated (+). DNA and RNA complementary to mRNA are designated (−), and double-stranded nucleic acid is designated as (±). The major viruses causing respiratory illness are found in Class I, which has a double-stranded DNA genome (e.g., adenovirus and the herpesvirus family), Class IV, which has a single-stranded (+) RNA genome (rhinoviruses and coronaviruses), and Class V, which has a single-stranded (−) RNA genome and includes influenza, parainfluenza, and RSV.

The DNA viruses replicate their genome in the host cell nucleus and send the mRNA to the cytoplasm, where the viral proteins are produced. These proteins then return to the nucleus, where the complete virus is assembled. With few exceptions, the respiratory RNA viruses replicate their nucleic acid, synthesize proteins, and assemble new viral particles entirely within the host cell cytoplasm. This difference accounts for the fact that the viral inclusions seen in infected cells with the light microscope are more common in the nucleus with DNA viral infection and in the cytoplasm with RNA viral infection. It is our contention

that viruses may contribute to the inflammatory process by latent infection where there is production of important viral proteins without replication of a complete virus and by persistent infection where there is continuous, low-level viral replication.

### A. Class I Viral Infections

*Adenovirus*

The adenovirus has the ability to produce bronchiolitis and bronchopneumonia (9,10) in children and young adults, and epidemiological studies monitoring seroconversion suggest that subclinical infections are common during an epidemic. Although Smith et al. (1) did not find that adenovirus was associated with acute respiratory illness, there are good theoretical reasons to believe that latent adenoviral infections are capable of amplifying an inflammatory process in the distal airways and contributing to both acute and chronic disease in COPD.

The adenovirus has an icosahedral shape (20 triangular faces, 12 apices, and 30 edges) with an outer coat that consists of 240 hexons (virion protein 2) and 12 penton bases (virion protein 3) located at the apices of the icosohedral structure (11). Infection begins when a fiber covalently linked to each penton base (virion protein 4) attaches to a specific receptor on the cell surface to allow the virus to become internalized. Once inside the cell, the capsid is stripped and the double-stranded DNA core is transported to the nucleus where the viral genes are transcribed. The "early" genes use host cell mechanisms to synthesize viral mRNA and proteins, which are important to subsequent viral DNA replication. The "late" viral genes are responsible for producing structural proteins, which are synthesized in the cytoplasm and transported to the nucleus for assembly of complete viral particles. During the late phase, host cell DNA, mRNA, and protein synthesis are shut off and the cell becomes devoted to the synthesis of the virus. During an acute infection, the viral yield per cell can rise from zero to $10^4$ plaque-forming units in 30–35 hours (11).

Figure 3 shows a histological specimen prepared from a study of post-mortem lung where death was due to acute adenoviral infection (12). It shows the histology of a peripheral bronchiole where the hematoxylin and eosin–stained section provides evidence of epithelial damage and the presence of an inflammatory exudate in the lumen. An in situ hybridization study of this tissue performed using a probe for the entire length of adenovirus 5 show that many of the airway epithelial cells are loaded with adenovirus.

Matsuse and colleagues observed that portions of adenoviral genome could be found in the lungs of heavy smokers who do not have acute infection (13). They also found that some of the early regions of the adenoviral DNA were present in excess amounts in the airways of patients with COPD and speculated that proteins produced from this viral DNA could contribute to the inflammatory process in

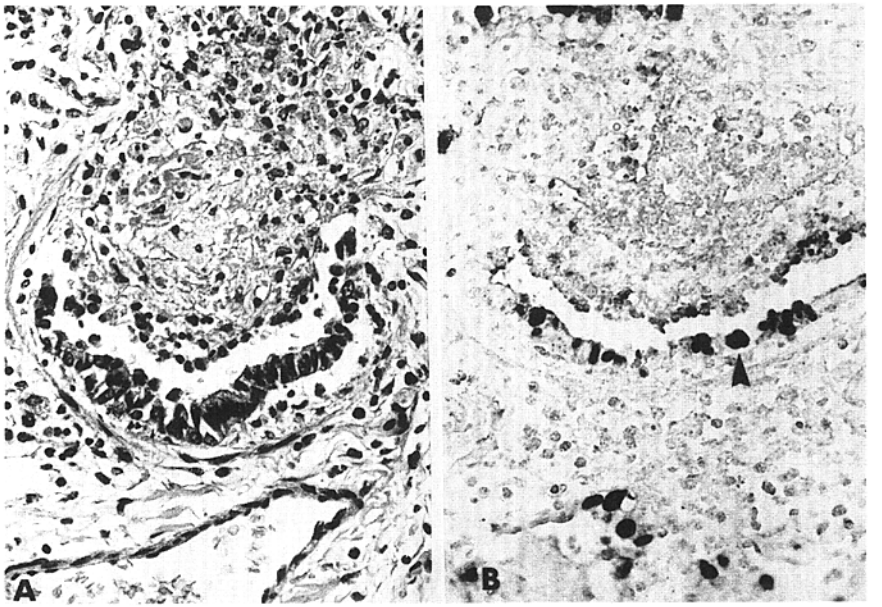



**Figure 3** Histological changes produced in the lung by an acute lytic adenoviral infection in a child: (A) H&E section showing severe bronchiolitis with an organizing intraluminal exudate; (B) in situ hybridization study performed on this tissue where the black dots represent cells heavily laden with adenoviral DNA (original magnification ×250). (From Ref. 12.)

COPD. To understand how this might work requires further consideration of some of the features of the adenoviral genome and the sequence in which it is expressed.

The first genes expressed during an infection code for proteins are required to carry out a number of key regulatory functions needed to assemble a new virus (Fig. 1). These early genes (14,15) are grouped into six transcription units, denoted E1A, E1B, E2A/B, E3A/B, E4, and L1 early. Liu and Green have recently shown that the E1A protein is capable of activating a large number of host genes (16). In acute infection, the E1A protein turns on the host cell to facilitate viral replication. Expression of the E1A/E1B region of the adenovirus is also capable of transforming cells and causing them to proliferate indefinitely. This allows the virus to affect cells without the need for assembly of complete viral particles. Proteins encoded in the E1A region have been shown to have other interesting functions including the ability to interfere with normal inhibitors of cell division and growth and to sensitize cells for destruction by cytokines such as TNF.

The E3 region encodes nine overlapping mRNA with different splicing

patterns. One of these proteins, the E3/19K, is capable of blocking the expression of the Class I MHC molecule by the infected cell, which allows the cell to evade destruction of cytotoxic T lymphocytes (17,18). Studies showing that the E3/19K protein has different affinities for Class I antigen indicate that the pathogenicity of a given adenovirus serotype could be influenced both by the virus and by the host MHC haplotype (16). This mechanism serves to protect the adenovirus by preventing destruction of the host cell by the cytotoxic lymphocytes. These protected cells provide an opportunity for the virus to continue to use the host cell to grow and multiply and to produce a latent infection in the host cell.

A normal gene is associated with both a proximal promoter and activator sequences that assist in regulating the transcription of the gene. The proximal promoter has been likened to the ignition of a car that turns on transcription at a low level when the RNA polymerase and other factors bind to it. The low rate of transcription induced by the primary promoter can be accelerated when another set of protein transcription factors interact with DNA-binding sites located either upstream or downstream from the primary promoter. The E1A protein can function as a ubiquitous promoter of many host genes by interacting with the DNA-binding site of these transcription factors. Elliott and associates (19) have recently shown that the E1A protein is expressed in human lungs that are latently infected by the adenovirus, and we postulate that this type of latent infection could contribute to COPD by amplifying the genes that cause the inflammatory process.

### *Herpesvirus Family*

The herpesvirus family includes the herpes simplex viruses (cold sores and genital herpes), varicella-zoster virus (chickenpox and shingles), cytomegalovirus (an opportunistic pathogen), the Epstein-Barr virus (infectious mononucleosis), and human herpesvirus type 6 (roseola). All of these viruses cause latent infections, which can be reactivated into acute disease.

The pattern of replication is consistent with DNA viruses, where the genome is replicated in the nucleus. The capsid proteins are synthesized in the cytoplasm and the complete virus is assembled in the nucleus. Accumulation of assembled viruses within the nucleus is responsible for the characteristic inclusion bodies, which rearrange the chromatin and from a clear ring around the periphery of the nucleus. The viral envelope is acquired as the virus pushes through the nuclear membrane, in contrast to RNA viruses, which acquire an envelope from the plasma membrane.

#### Herpes Simplex Virus

Herpes simplex virus type I infection is usually acquired as a nasopharyngitis in infancy but can affect the eye and occasionally spreads to the central nervous system (CNS) to produce meningitis and encephalitis, which is associated with a high mortality with mental defects in survivors. Following the initial infection, the

virus persists for the life of the host and commonly produces the cold sores (herpes labialis) that recur in febrile illnesses such as influenza and meningococcal infections (20). During the latent period, the virus remains in the sensory nerve ganglia and, when reactivated, can reemerge down the sensory nerve to the epidermis and produce the characteristic herpes skin lesions.

The herpes simplex virus can also infect the respiratory tract of patients with severe underlying disease, particularly in individuals who have severe burns and in alcoholics. Tracheobronchitis with or without parenchymal involvement has been found in a number of patients with the adult respiratory distress syndrome (ARDS) of various etiologies. However, in most of these cases, herpes simplex virus would seem to be a secondary invader rather than the cause of the ARDS. The lesions in the tracheobronchial tree are characterized by necrotic ulcers covered with a fibrinopurulent exudate, and the parenchymal lesions are characterized by nodular foci of necrosis and hemorrhage. In a study of patients with COPD by Smith et al. (1), herpes simplex was found as frequently in patients free of respiratory illness as it was during an episode of illness, suggesting that acute infections did not cause the respiratory symptoms. However, this does not rule out the possibility that latent infection might contribute to the inflammatory process that precipitates the respiratory failure.

### Varicella-Zoster Virus

The varicella-zoster virus produces chickenpox, which is one of the common major exanthemous diseases of childhood (21). The infection spreads by droplets, multiples in the upper respiratory tract, and spreads to the regional lymph nodes before entering the blood stream. The viremia results in skin infection where the virus produces a characteristic vesicular rash, which is usually followed by recovery and immunity. The virus remains latent in nerve ganglia and can be reactivated to produce skin lesions, which are confined to the dermatomes associated with the infected ganglia (herpes zoster, shingles). When primary varicella occurs in adults, a radiographic pneumonitis is common and histological examination of the lung parenchyma shows foci of hemorrhagic necrotizing inflammation with diffuse alveolar injury where viral inclusion bodies can be identified. When these lesions heal, they become rounded fibrous scars with central calcification but do not contain inclusion bodies because there is no active viral replication.

### Cytomegalovirus

The cytomegalovirus (CMV) is perhaps the most widespread member of the widely distributed herpesvirus family (22). The majority of adults have serum antibodies against CMV, indicating that they have been exposed to one of the serotypes at some time. The natural reservoir of the virus is in humans, but the relationship between host and virus is symbiotic and the vast majority of infections remain subclinical. Both primary infections and reactivation occur in an

endemic fashion and in certain clinical settings produce disease in salivary glands, genitourinary tract, liver, and lung. The virus can also be transmitted by blood, where it can be commonly isolated from polymorphonuclear neutrophils (PMN), less frequently from monocytes, and occasionally from T lymphocytes, and it is frequently responsible for a mononucleosis–type clinical picture in the posttransfusion setting. CMV infection can become a major problem in immunocompromised patients, particularly in HIV-infected individuals and in organ transplant recipients treated with immunosuppressive drugs or radiotherapy. Bone marrow transplant recipients are particularly susceptible to CMV infections associated with prolonged viremia. The virus has also been implicated in the pathogenesis of a highly lethal pneumonia responsible for the severe respiratory failure that develops in the early phase of bone marrow transplantation. However, the bronchiolitis obliterans seen in the transplant setting occurs as a later complication and is probably more closely associated with graft-versus-host disease than with CMV infection.

Although Smith et al. (1) did not identify CMV infections in any of the acute episodes of respiratory illness in patients with COPD, this does not rule out the possibility that latent CMV infection might interact with an inflammatory process already present in the lung to produce acute disease.

### B. Class IV Viral Infections

The single-stranded (+) RNA viruses implicated in acute exacerbations of COPD include the rhinoviruses and the coronaviruses. These viruses are characteristically associated with self-limited, upper respiratory tract infections, but they can also be associated with acute lower respiratory tract infections (23). These associations have generally been based on positive viral cultures in the nasopharyngeal secretions of symptomatic patients, and there is a surprising paucity of data available on attempts to directly identify these organisms below the level of the epiglottis. Smith et al. (1) found a statistically significant relationship between the presence of rhinoviruses and coronaviruses and acute respiratory illnesses in their study of patients with COPD; however, it is less clear whether they can cause acute respiratory failure.

#### *Rhinovirus*

Well over 100 serotypes of human rhinoviruses have been characterized from the time of their discovery in the 1950s. Rhinoviruses are amongst the smallest human pathogens, consisting of an isometric, nonenveloped virion measuring 24–30 nm in diameter. Rhinovirus capsid has icosohedral symmetry, with 32 capsomeres surrounding a core containing single-stranded RNA. A major advance in our understanding of rhinoviral infections is the discovery of intercellular adhesion molecule-1 (ICAM-1) as the major cell surface receptor for rhinoviruses (24).

ICAM-1 is an important leukocyte adhesion molecule, originally described on vascular endothelial cells, which mediates adhesion of neutrophils, lymphocytes, and monocytes. The discovery of ICAM-1 as the major rhinoviral receptor has resulted in development of innovative strategies (e.g., soluble ICAM-1) for prevention or alleviation of acute rhinoviral infections (25). Whether such strategies can prevent or alleviate rhinoviral-induced acute respiratory illness in patients with COPD remains unknown.

Nasal mucosal biopsies from rhinoviral-infected individuals are typically unimpressive with respect to epithelial cell lysis or mucosal inflammation, and the mechanisms by which rhinoviruses can precipitate acute exacerbations of COPD remain unclear. A crucial unresolved issue is whether the rhinovirus remains confined exclusively to the upper respiratory tract during these acute exacerbations, or whether the virus can spread into the intrapulmonary airways and directly contribute to structural and functional alterations, as described in Chapter 2. If the virus remains confined to the upper respiratory tract during acute exacerbations of COPD, rhinovirus may potentially produce "action at a distance" by recirculation of antigen-presenting cells and virus-specific lymphocytes from the nasopharynx through the bronchial and pulmonary circulations. Theoretically, this could stimulate the release of a myriad of inflammatory cytokines and related molecules to produce disease at the distant site. Similar mechanisms also could be applicable to rhinoviral-induced acute exacerbations of asthma (26).

#### *Coronavirus*

Coronaviruses were discovered in 1965 at the Common Cold Unit in England as a consequence of failed attempts to culture rhinoviruses from patients with upper respiratory tract infections. In contrast to the rhinoviruses, the coronaviruses are comparatively large (70–120 nm in diameter), enveloped particles that have distinctive "tulip petal"–shaped surface projections. Serotypes 229E and OC43 commonly infect humans. The virus replicates in the cytoplasm of infected cells and matures by budding into the cisternae of the endoplasmic reticulum and Golgi apparatus. Upon release, mature virions spread to adjacent cells by adhering strongly to their cell membranes. Although the coronavirus has been linked to acute episodes of respiratory illness in patients with COPD (1,27), mechanisms by which the virus contributes to these acute exacerbations of respiratory illness remain unclear. As they are apparently confined to the upper respiratory tract, coronaviruses could precipitate acute lower respiratory tract disease in a manner similar to that postulated for the rhinoviruses.

### C. Class V Viral Infections

The orthomyxoviridae (e.g., influenza viruses) (28) and paramyxoviridae [e.g., parainfluenza (29) and RSV (30)] have single-stranded (−) RNA genomes. A

major difference is that the genome of the influenza virus is segmented, whereas that of the parainfluenza virus and RSV are not. The segmental nature of the influenza virus is important because it facilitates genetic recombination that does not occur to nearly the same extent in the parainfluenza or respiratory syncytial viruses.

### *Influenza Virus*

The genome of the influenza virus consists of a single strand of RNA divided into eight segments, which are surrounded by capsid protein. In the major influenza viruses, types A and B, there are eight segments and 10 viral proteins, the extra two proteins being generated by splicing the message for the M protein (segment 7) into three. Classification is based on the internal antigens of the M and nucleocapsid proteins and allow three independent non–cross-reacting types of influenza virus to be recognized. Strains of influenza type A are found in humans and animals, whereas B and C are restricted to humans. The segmented nature of the influenza virus genome allows RNA segments of two viruses to recombine into a new virus when they coinfect a single cell. This type of genetic recombination and reassortment is the basis for the new viral strains and species and accounts for the antigenic drift and shift seen in the influenza viruses.

Influenza viral infection is probably the most important respiratory disease in humans. It is spread by droplet infection and readily establishes infection in the upper respiratory tract prior to extending into the lower airways. The neuraminidases expressed on its surface allow the virus to penetrate the mucus layer of the respiratory tract and attach to the cell surface, where it internalizes and replicates. In uncomplicated influenza infections, bronchoscopic examination of the lower respiratory tract has shown that there is diffuse reddening and swelling of the larynx, trachea, and bronchi. Light microscopic examination of the tissue shows evidence of damage and desquamation of the epithelium frequently exposing a thickened and sometimes hyalinized basement membrane. There is also evidence of submucosal edema with vascular congestion and infiltration of neutrophils and mononuclear cells. Viral antigen can be demonstrated in the epithelial cells and mononuclear cells and occasionally in the basal cell layer. Later in the course of the disease, reparative and destructive processes may be present simultaneously with complete resolution of the epithelial necrosis occurring over a period of weeks to months. The small peripheral airways are often affected in uncomplicated infection, and abnormalities in peripheral airway function may persist long after the symptomatic illness has subsided. However, in uncomplicated infection there is usually little permanent damage to the lung even in patients with chronic obstructive lung disease. However, in some settings, the virus can also produce a lethal pneumonia associated with diffuse alveolar injury and

hemorrhagic edema. The edematous phase is followed by formation of hyaline membranes and a slow progressive recovery that can be prolonged.

Infection of the respiratory tract with influenza virus predisposes the host to bacterial infection of the bronchial tree by interfering with mucociliary clearance and the killing of bacteria by alveolar macrophages and by increasing the aspiration of bacterial laden mucus exudate from the upper airways. The most common bacterial infections complicating an attack of influenza are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. The symptoms of this bacterial infection may be indistinguishable from primary viral pneumonia, except that bacterial pneumonia is more frequently associated with pleuritic chest pain and shaking chills. Combined viral and bacterial infections are probably responsible for many episodes of acute respiratory failure in patients with COPD, but much of the pathophysiology of these infections remains to be elucidated.

### *Parainfluenza and Respiratory Syncytial Virus*

The parainfluenza (29) and respiratory syncytial viruses (30) are also major causes of lower respiratory tract disease. They differ from the influenza virus in that their negative single-stranded RNA genome is nonsegmented. They also have a helical nucleocapsid surrounded by a lipid envelope. Both of these viruses have the ability to cause cell fusion, giving rise to typical multinucleated giant cells or syncytia observed in vitro. They also have the ability to establish persistent infection in cultures in which the infected cells survive for long periods, while the virus is continuously replicated at low levels that do not produce a typical cytopathic effect. Whether or not this persistence also occurs in vivo is less clear, but if it did, it could be an important reservoir of disease.

Four serologically distinct types of parainfluenza virus produce infections of the human respiratory tract, the most dangerous of which is an acute laryngotracheobronchitis, or croup. They are also capable of producing lower respiratory tract infection similar to influenza which can be complicated by secondary bacterial infection in the same way.

RSV differs from the influenza and parainfluenza viruses in that it does not express either hemagglutinin or neuraminidases (30). It produces severe life-threatening lower respiratory tract disease in infants and children, where it is particularly severe under the age of 6 months (Fig. 4). Adult infections tend to be milder and confined to the upper respiratory tract, although it is a significant cause of viral bronchopneumonia, which can be complicated by secondary bacterial pneumonia. The fact that infants are particularly susceptible during the period when they have circulating maternal IgG antibodies but lack the ability to produce their own local IgA protection has implicated antibody-mediated hypersensitivity in the pathogenesis of the bronchiolitis. The concept that IgG contributed to the

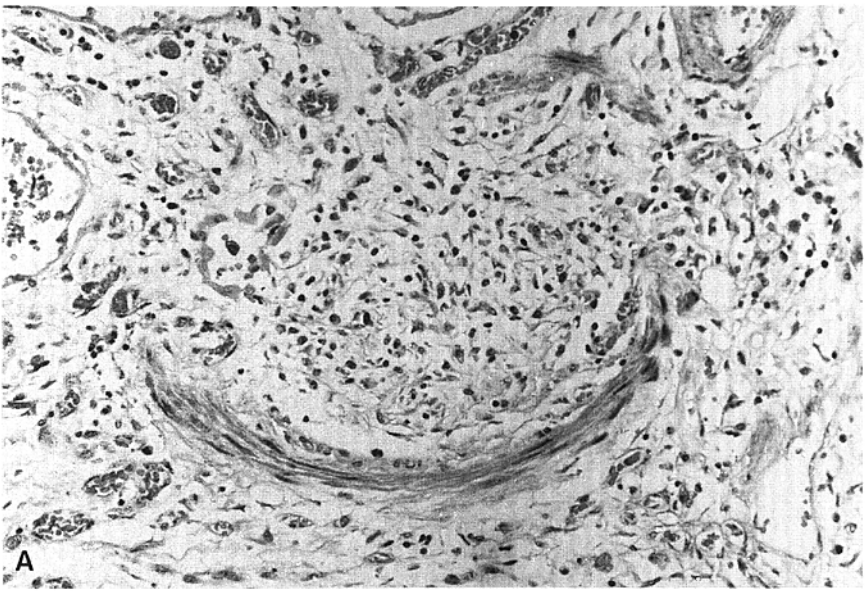
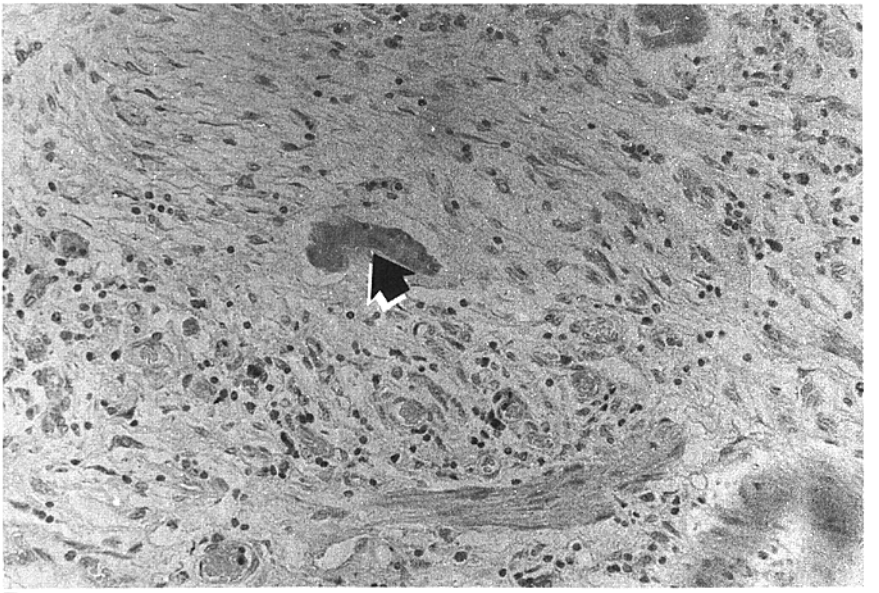



**Figure 4** Histological changes produced in the lung of an infant who died of acute RSV bronchiolitis: (A) H&E section of a membranous bronchiole showing extensive epithelial cell necrosis, predominantly mononuclear cell inflammation through the full thickness of the airway wall and considerable intraluminal exudate; (B) intensely positive immunohistochemical staining for RSV protein within sloughed bronchiolar epithelial cells (arrow). (Hematoxylin counterstain, original magnification ×250.)

bronchiolitis was further supported by an adverse experience where the administration of a formalin-inactivated vaccine that produced an IgG response in newborns resulted in a more severe bronchiolitis in these children when they were naturally infected in a subsequent epidemic. These findings suggest that the formation of IgG–virus complex in the airways could play an important role in the pathogenesis of this form of bronchiolitis and raises the possibility that the host immune system might interact with a virus to produce a chronic organizing bronchopneumonia in some adults.

## V. Summary

This very brief overview of viral respiratory tract infections outlines the mechanisms that might contribute to acute respiratory failure in patients with COPD. To date, most studies have focused on the effect of acute lytic infections. However,



(B)

**Figure 4** Continued

there is a good chance that the inflammatory process responsible for COPD may be influenced and perhaps enhanced by the persistent and latent infections that follow these acute episodes. Although there is no clear evidence that these mechanisms contribute to episodes of acute respiratory failure, they deserve to be explored because they might provide us better insights into how to deal with this difficult problem.

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# 12

## Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

### Bacterial Infection as a Precipitating Factor

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Infection is usually considered to be the main cause of acute exacerbation in chronic obstructive pulmonary disease (COPD) patients, "accounting for 90 percent of cases in which a triggering factor can be demonstrated," as indicated in several well-known textbooks (1–4). Since the early 1950s, a considerable body of data has been collected associating bacteria with purulent sputum and exacerbation of chronic bronchitis. Despite numerous studies, the precise role of infection in COPD has yet to be elucidated. Bacterial infection does not appear to initiate the disease except possibly in patients with a history of frequent childhood respiratory infections (5–7). However, bacteria are probably significant in perpetuating the disease and may be at the origin of the characteristic exacerbations (8–10).

COPD is characterized by irreversible damage to the lungs and airways. By contrast, infection is one of the more treatable and preventable diseases. Thus, the definition of an infective element in any chronic and incurable disorder opens up new possibilities for therapy and prevention that need to be fully explored. The precise causes of acute respiratory failure (ARF) are essentially unknown (11). Precipitating factors are multiple and probably interrelated. Besides infection, there are several other commonly evoked causes of ARF including iatrogenic factors, such as the use of respiratory depressants or uncontrolled oxygen therapy, pneumothorax, pulmonary embolism, the postoperative or posttraumatic period,

and increased atmospheric pollution (12,13). Thus, the first aim of this chapter is to review and evaluate current clinical concepts of the specific role of bacterial infection in ARF in COPD patients by reviewing conflicting results in the literature concerning the presence of bacteria during exacerbation and stable periods and the efficacy of antibiotics in preventing respiratory failure and controlling symptoms.

Acute respiratory failure in COPD patients is one of the most frequent causes of admission to the intensive care unit (ICU). Even though endotracheal intubation and mechanical ventilation are not indicated in all patients, many COPD patients admitted to an ICU undergo this treatment (14), as it allows rapid improvement in gas exchange and easy suction of secretions. However, it exposes patients to a variety of complications such as nosocomial infections, gastrointestinal bleeding, and arrhythmias and also to secondary problems linked to the complications of intubation such as pneumothorax and ventilator-associated pneumonia (15,16). As lung infection could be the cause of ARF in COPD patients, it (i.e., nosocomial lung infection) could be the consequence of ARF in hospitalized COPD patients and affect the prognosis of such patients (17,18). The second aim of this chapter is to specify the characteristics of ventilator-associated pneumonia in COPD patients who are ventilated because of acute respiratory failure.

## I. Role of Bacterial Infection and Antibiotics in ARF in COPD Patients

The uncertainty concerning the role of bacterial infection in ARF in COPD patients is a reflection of the confusing and conflicting data on the role of tracheobronchial microflora and the usefulness of antibiotics in treating this disease (5,10,19,20). Much of the confusion and conflict in the data is due to several problems and limitations in the studies evaluating this role.

### A. Limitations

In this review, we use the term COPD as defined by the American Thoracic Society (21). It has been pointed out previously that patients who fulfill the criteria for this diagnosis represent a heterogeneous population with a broad spectrum of diseases including emphysema, peripheral airway disease, and chronic bronchitis (22). A large majority of epidemiological and therapeutical studies have been conducted in patients with chronic bronchitis without evaluating the severity of the disease, and some of these were limited to patients with emphysema or included patients with asthma (23).

There is no universally clear-cut definition of acute respiratory failure in COPD patients. Moreover, there is no universally accepted definition of "acute

exacerbation" from "the onset of symptoms suggestive of upper or lower respiratory infections or any worsening of dyspnea" until "an alteration of the quiescent state of the patient with an increase in either the quantity or the purulence of the sputum" (1). Therefore, depending on the definition used, evaluation of the role of infection can differ. Furthermore, most of the data were obtained from groups of patients with stable bronchitis or outpatients during moderate exacerbations of COPD (24). The problem has been poorly investigated in patients with severe exacerbation or during real acute respiratory failure, especially when mechanical ventilation is needed (25).

The term infection implies "the pathologic establishment and replication of microorganisms in the tissues of a host" (26). Host response to infection is highly variable, depending on the interrelationship of many host and agent factors, and ranges from subclinical or inapparent infection to disease. Colonization indicates the presence of an organism without clinical or subclinical disease (26). However, in this case, the organism that is replicating in or on tissues of the host can also be identified by culture in the laboratory. Therefore, patients with COPD may be infected, although not clinically symptomatic or colonized, with signs of acute exacerbation. Since the diagnosis of exacerbations of COPD is based on symptoms and because most respiratory infection is inferred clinically rather than proven microbiologically, the differentiation between infection and colonization is not possible with usual laboratory tests. It is difficult to determine if an exacerbation is, in fact, produced by infection.

In the process of searching for infectious causes of acute exacerbation, the respective parts of viral infections, including mycoplasma, chlamydia and bacterial infections, should be assessed. In particular, viral infection has been postulated as a potential catalyst for bacterial infection in the most severe cases of acute exacerbations (27,28).

Evaluation of the role of bacterial infection in COPD patients is based on the analysis of pathogens present in the lower respiratory tract. One possible explanation for the conflicting results is the methods used to evaluate infection of the trachea, bronchi, and/or lung parenchyma. Almost all epidemiological studies were conducted using expectorated sputum. Culturing sputum or aspirated material from the trachea tells us little about the small airways because of the frequent contamination by pathogens colonizing the upper respiratory tract or the trachea in COPD patients. Moreover, many epidemiological studies claiming an association between some infective agents and acute exacerbations can be criticized because they are based on organisms isolated from hospitalized patients several days after the onset of illness, by which time the primary infecting agent may have been replaced by secondary invaders.

Finally, assessing the efficacy of antibiotic therapy in acute exacerbation of COPD is difficult because of the natural history of the disease. Patients typically have a waxing and waning course, and many exacerbations improve with suppor-

tive therapy that does not include antibiotics (29). Moreover, results of therapeutic studies conducted using a particular antimicrobial agent could probably not be extended to all patients, all types of exacerbation, and all drugs.

### B. Consequences of Infection

The prognosis of COPD is affected by some important variables, as indicated by Hudson (30). Although there are no firm data to support the following points, it is reasonable to suggest an association between a high mortality rate and (1) the severity of underlying COPD, (2) the severity of the acute precipitating illness, including infection and especially pneumonia, (3) the severity of the acute respiratory failure, and (4) the development of complications during acute respiratory failure, especially nosocomial pneumonia.

The important role played by infection in the course and prognosis of COPD patients has been confirmed by Burrows and Earle (31), who studied the causes of death in a group of 200 COPD patients over a 7-year period. The 5-year mortality rate was 47%. This study reported that most deaths were directly attributable to the underlying lung disease or one of its complications. Respiratory infection (including acute respiratory infection and nosocomial pneumonia) was the most often identified cause of death, accounting for 20% of the total. By contrast, 5.5% died of pulmonary embolus, 4.6% of sudden death including myocardial infarctus, 7.3% of neoplasm, and 1.9% of suicide. In about 40% of cases, no obvious precipitating factors were observed despite the use of autopsy and careful examination of terminal clinical course as bases for diagnosis.

In addition to its role in causing death, infection has a major impact on expenditures for medical care of COPD patients. It is generally accepted that the cost of drugs used in the treatment of chronic bronchitis is nearly 30% of the total cost of drugs used in all respiratory diseases ($305 million in the 1970s) and that a major proportion of these drug costs was for antibiotics (3). Besides the economic burden of antibiotics, their role in nosocomial infection (32) and selection of resistant bacteria (33) are major contributors to the outcome of COPD patients.

Since infection seems to be a major determinant of the outcome of COPD patients and since antibiotics constitute one of the major classes of pharmaceutical agents used in such patients, for purely economic reasons, as well as scientific ones, the precise role of bacterial infection and the validity of the use of antibiotic agents should be reassessed.

### C. Role of Bacteria in Nonpneumonic Exacerbation

#### *Comparison of the Role of Bacteria During Acute Exacerbation and Stable Period*

The role of bacteria can be evaluated by using microbiological analysis of secretions that reflect the entire respiratory tract (sputum), the lower respiratory tract

(transtracheal aspiration), or the distal respiratory tract (protected specimen brush) or by using serological tests.

### Sputum Examination

It is generally accepted that the bronchi of nonbronchitis patients without other lung diseases are almost always sterile, although culture methods are not perfect and may include oral flora (2,34). By contrast, pathogenic bacteria can be cultured from the bronchi of a large number of chronic bronchitis patients. In the early 1950s, May cultured bacteria from all 24 specimens of muciform sputum and in all 30 specimens of purulent sputum collected from 54 bronchitic outpatients (35,36). Considering the sole "potential pathogens," 54.2% of muciform sputa and 90% of purulent sputa were positive. *Haemophilus* spp. and *Streptococcus pneumoniae* were found in 95% of these positive cultures.

As indicated in Table 1, these bacteriological results were confirmed by several studies conducted in patients with COPD (35,37–39). These studies, based on sputum cultures, found that more than 60% of cultures were positive in patients with stable chronic bronchitis and that *S. pneumoniae* and *Haemophilus influenzae* were isolated in most cases. One or both of these species can be rightfully considered as baseline microbial flora in many patients with COPD. McHardy et al. compared tracheobronchial microflora during acute exacerbation and stable periods using sputum examination (40). They compared 77 exacerbations with 628 routine specimens in 38 patients and found no difference in the number of positive sputum cultures during exacerbations and stable periods (30% and 22%, respectively; NS). Moreover, pathogenic bacteria were equally present during exacerbations and quiescent periods: *H. influenzae* (12% vs. 11%; NS), *S. pneumoniae* (14% vs 8%; NS), *H. influenzae* associated with *S. pneumoniae* (3% vs 2%; NS).

Thus, as shown by sputum cultures, chronic colonization of the airways with *H. influenzae* and *S. pneumoniae* occurs in a large number of COPD patients. The organisms are often found in the sputum during quiescent periods and the frequency of recovery is not greatly increased during acute episodes except when acute exacerbation is defined as an acute infectious exacerbation. In a study conducted by Medici and Chodosh in 38 patients with COPD (41), the numbers of all bacteria at direct examination and the numbers of each of the potentially bronchopathogenic microorganisms are significantly higher during acute infectious episodes ($100.8 \pm 178.5$ per oil immersion field) than during stable periods ($6.2 \pm 14.0$) and postinfection periods ($16.9 \pm 32.0$).

### Transtracheal Aspiration

The major limitation of epidemiological studies conducted in COPD patients is related to the sampling method used for detecting lower respiratory tract microflora and diagnosing infection. Sputum examination and sputum culture are the main methods of easily determining the presence of bacteria in the respiratory

**Table 1** Literature Review of the Results of Culture of Sputum in Case of Stable Chronic Bronchitis[a]

| Authors (Ref.) | No of patients (*n*) | No of specimens (*n*) | *Streptococcus pneumoniae* (%) | *Haemophilus influenzae* (%) | *Streptococcus haemolyticus* (%) | *Staphylococcus aureus* (%) | Gram-negative bacteria (%) |
|---|---|---|---|---|---|---|---|
| Stuart-Harris (37) | 113 | 172 | 50.5 | 15.0 | 4.7 | 11.5 | 5.3 |
| Brown et al. (38) | 20 | 83 | 73.5 | 50.6 | 25 | 10 | 14.4 |
| May et al. (35) | 54 | 54 | 57.4 | 25.9 | — | 13 | 13.4 |
| Miller et al. (39) | | | | | | | |
| Mucoid | 110 | 110 | 35 | 40 | 32 | 5 | 7 |
| Purulent | 20 | 20 | 45 | 70 | 20 | — | 5 |

[a]Sum of percentage might exceed 100% owing to polymicrobial flora.

tract. Unfortunately, sputum is an impure sample of tracheobronchial secretions because of frequent oropharyngeal contamination (42) and the inability to collect an adequate sputum sample, particularly in cases of acute exacerbation or during acute respiratory failure (43).

Transtracheal aspiration (TTA) has been described as a means to obtain specimens from the lower respiratory tract that are free of contamination by the normal flora of the upper airways (44). This procedure has proven useful for studying the microbiology of lower respiratory tract infection (45,46). In COPD patients, TTA could theoretically be the means for distinguishing between bacteria colonizing the upper respiratory tract and bacteria colonizing or infecting the lower respiratory tract. However, in current clinical practice, TTA is rarely used for diagnosing lower respiratory tract infection.

Irwin et al. (47) evaluated the tracheobronchial microflora of a homogeneous group of clinically stable patients with COPD. They demonstrated that a bacterial tracheobronchial microflora was present in only 50% of the 20 studied patients. By contrast, sputum cultures were positive in all cases. Moreover, the mean number of bacteria isolated per patient was 2 using sputum cultures and 0.5 using TTA cultures. Finally, organisms isolated by the two techniques were only partially concordant. This study demonstrates that the use of sputum cultures, rather than TTA, not only would have inaccurately characterized the tracheobronchial microflora, but also would have failed to discover that 50% of studied patients had a sterile lower respiratory tract.

The difference in microbiological data between stable periods and acute episodes has never been evaluated prospectively using TTA in a homogeneous group of COPD patients. However, two different studies have used TTA to evaluate tracheobronchial microflora: one in patients during stable period (48) and the other in patients during acute exacerbation (49). The main results of these two studies are shown in Table 2. Even if the comparison is of limited value because of potential differences in the studied populations, the similarity of the results

**Table 2** Results of Culture of TTA in Patients with Stable Chronic Bronchitis and in Patients with Acute Exacerbations

| Authors (Ref.) | Condition | No. of patients | No. of positive TTA (%) | Isolated pathogens | |
|---|---|---|---|---|---|
| | | | | First rank (%) | Second rank (%) |
| Haas et al. (48) | Stable | 24 | 21 (87.5) | *H. influenzae* (25) | *S. pneumoniae* (21) |
| Schreiner et al. (49) | Acute exacerbation | 87 | 78 (87.3) | *H. influenzae* (35) | *S. pneumoniae* (22) |

obtained in these two groups of patients is obvious, with 87.5 and 87.3%, respectively, having positive TTA cultures. Moreover, in these two studies, it is worth noting that patients with bacteria cultured from TTA were clinically indistinguishable from patients with negative TTA cultures. Thus, the use of accurate sampling techniques confirms that potentially pathogenic organisms can be recovered from the respiratory tract secretions of virtually all patients with COPD at some time during the course of their disease.

### Protected Specimen Brush

The patient with COPD does not have sterile airways, as shown by sputum examination, or a sterile trachea, as shown by TTA cultures, even when there is no clinical evidence of infection. Another question concerns the accurate assessment of the flora in the small airways of these patients. The use of sampling techniques such as the protected specimen brush, as described by Wimberley et al. (50,51), or the bronchoalveolar lavage (52,53) may lead to a more accurate description of the pathogens associated with distal bronchial infection in acute exacerbations of COPD (54). Unfortunately, studies using BAL with this as the objective have not been reported, and studies focusing on the analysis of distal microflora in COPD patients with the use of a protected specimen brush (PSB) are rare. Pollock et al. evaluated the PSB in a series of 144 patients (55), 11 of whom had bronchitis, which was defined as severe exacerbation of preexisting lung disease with an increase in purulent sputum production. All 11 patients had at least one organism in amounts $\geq 10^3$ cfu/ml that grew from their PSB. *H. influenzae* was the predominant organism isolated from 8 patients.

The study conducted by Fagon et al. (56) is the sole study specifically dedicated to identifying bacterial aetiology of acute respiratory failure requiring mechanical ventilation in COPD patients using a valid invasive technique. To overcome the major problem of contamination by upper respiratory tract secretion, particularly following intubation, and to take into account the possibility of a real difference in the resident flora at different levels of the tracheobronchial tree (57), the authors chose to perform fiberoptic bronchoscopy using a protected specimen brush. Fifty-four patients who had not received antibiotics during the 5 days preceding admission to the ICU were investigated. In 27 (50%) PSB cultures were negative, and in 27 (50%) PSB cultures revealed at least one microorganism at a concentration of more than $10^2$ cfu/ml. Quantitative cultures revealed that more than 40% of isolated bacteria were found in low concentrations ($\leq 10^3$ cfu/ml). A total of 44 microorganisms were cultured in 27 patients. *Haemophilus* spp. were the most often isolated pathogens (39%), and streptococci accounted for 25% of all bacteria (including *S. pneumoniae* in 16% of cases). In 11 patients, more than one bacterial species were isolated from PSB cultures. Finally, the 27 patients with positive PSB cultures could not be clinically distinguished from the 27 patients with sterile PSB cultures. This study clearly indicates that distal

bronchial infection, as evaluated by PSB before the administration of antibiotics, is not the predominant cause of acute respiratory failure in COPD patients.

### Serological Studies

Documenting a serological response to an organism has been considered a valid method for demonstrating the existence of infection with that organism (26). The evaluation of infection in patients with COPD has been helped by serological aids, and several studies have used this approach to investigate exacerbations of COPD. The results, however, are equivocal.

To evaluate the potential role of *H. influenzae* in exacerbations, COPD patient and control series have been assayed for antibody level in spite of the low relevance of serological methods for nonencapsulated strains. Some studies have shown no difference between COPD patients and controls (58). Other studies showed higher antibody titers to nontypable *H. influenzae* in COPD patients, but no relationship to exacerbation (59,60). Other studies showed a rise in antibody titer after exacerbations (61,62), which could be partly due to antigenic similarities with unrelated bacteria. Despite limitations due to the use of serological methods that have not been fully evaluated, these results do not provide clear evidence of the role of *H. influenzae* in acute exacerbations.

Similar but much less clear-cut results were obtained for *S. pneumoniae*. Burns (63) demonstrated that antibody against pneumococcal C polysaccharide, a phosphocholine-containing polysaccharide common to all pneumonococcal serotypes, was present in 13% of patients with chronic bronchitis and 27% of patients with mucopurulent or obstructive bronchitis. In evaluating 56 exacerbations of chronic bronchitis, Reichek et al. (62) measured IgM antibodies to *S. pneumoniae* in 11 patients and found a fourfold increase in 3 of them. Similarly, Lambert and Stern (64) found development of serum antibody to *S. pneumoniae* in only 2 out of 30 acute exacerbations of COPD.

Little success has been met in attempting to clearly define the role played by *Mycoplasma pneumoniae* in patients with chronic bronchitis. In a study conducted by Chery et al. (65), *Mycoplasma* spp. were recovered at the same frequency from 22 patients with chronic bronchitis as from 20 nonbronchitis patients. Eighty-three percent of the rise in antibody titers in patients with chronic bronchitis occurred during, or immediately following, acute respiratory attacks. Carilli et al. (66) found fourfold antibody responses to *M. pneumoniae* in only 4 out of 46 (8.7%) exacerbations. Similarly, Westerberg et al. (67), following 24 normal adults and 76 COPD patients during a 6-year period, demonstrated that only 1% of acute respiratory illnesses could be attributed to infection with *M. pneumoniae*; Ross et al. (68) described a similar isolation rate. These results suggest that mycoplasma may exist in the bronchi without causing symptoms and is unusually linked with an exacerbation of the disease. A recent study conducted by Beaty et al. (69) compared antibody titers against TWAR (*Chlamydia pneumoniae*) in COPD

patients. The results reported in Table 3 show that TWAR infection is rare in COPD patients with acute exacerbation as well as in those without exacerbation. In contrast, the majority of patients from both groups had serological evidence of previous *C. pneumoniae* infection.

Identification of antibody coating of bacteria in sputum has been suggested as a method of identifying bacteria responsible for chronic lower respiratory tract infection (70), using methods formerly suggested to differentiate upper from lower respiratory tract infection. Vereen et al. (71) demonstrated that all but one of 18 stable COPD patients had antibody-coated bacteria identified in brushings from lower respiratory tract secretions, a specificity similar to sputum cultures, which were positive in all 18 patients. This study demonstrated that bacteria present in patients with COPD may become antibody coated in the absence of clinical evidence of acute illness.

### *Relationship Between Viral Infection and Bacterial Infection*

The concept that viral infections of the respiratory tract may impair host defenses in a manner that would lead to increased colonization or infection with pathogenic bacteria has been supported by numerous laboratory and clinical studies (72–74). It has been postulated that interaction between viruses and bacteria may be important in the pathogenesis of chronic obstructive pulmonary disease (27,75). Nevertheless, the subject of viral–bacterial interactions in this population of patients has received little investigative attention.

The role that viral infection plays as a precipitating factor is the subject of another chapter in this book. The association of acute exacerbation with viral agents seems to be clearer than that with bacteria, with the strength of this association varying from high (28,66,76–78) to marginal (64,68,79–84). In a study evaluating interactions between virus and bacteria in patients with chronic bronchitis, Smith et al. (85) demonstrated that 102 of the 168 viral infections

**Table 3** Antibody against TWAR in Subjects with Acute Exacerbation of COPD (Group 1), with Stable COPD (Group 2), or without COPD (Group 3)

| | Group 1 ($n$ = 44) | | Group 2 ($n$ = 65) | | Group 3 ($n$ = 24) | |
|---|---|---|---|---|---|---|
| Antibody | (n) | (%) | (n) | (%) | (n) | (%) |
| Acute | 2 | 5 | 0 | 0 | 2 | 8 |
| Preexisting | 43 | 81 | 50 | 77 | 16 | 73 |

*Source*: Ref. 69.

diagnosed in this study were associated with the simultaneous isolation of *S. pneumoniae*, *H. influenzae*, or *H. parainfluenzae*. The main results of this study are shown in Table 4. The percentage of bacterial isolation associated with viral infections was similar to the overall rate of isolation of these bacteria, independent of viral infection (10.7 and 9.2% for *S. pneumoniae*; 13.7 and 12.8% for *H. influenzae*; 36 and 41.9% for *H. parainfluenzae*). The greatest association of specific viral infections with isolations of bacteria was between herpes virus infection and *H. influenzae*. In this study, the presence or absence of acute respiratory illness was not specified. In a study conducted in 86 acute exacerbations in patients not previously receiving antibiotics, Gump et al. (28) demonstrated that recovery of *H. influenzae* and *S. pneumoniae* was not significantly different in cases of virus-related exacerbation (67.7 and 35.5%, respectively) and those of non–virus-related exacerbation (50.9 and 38.2%, respectively). These studies suggest that, although viral infections seem to be partially responsible for acute exacerbations, they do not induce significant bacteria-related exacerbations.

### *Major Responsible Pathogens*

As repeatedly reported in a considerable body of data, *H. influenzae* and *S. pneumoniae* are by far the most commonly encountered pathogens in COPD patients during both stable periods and acute exacerbation. Recently, attention has been directed toward other bacteria such as *Branhamella catarrhalis* as potential

**Table 4** COPD Patients with Viral and Mycoplasmal Infection who had Simultaneous Bacterial Infection

| Virus or mycoplasma | No. cultured for bacteria | No. (%) of patients with bacteria | | |
|---|---|---|---|---|
| | | *S. pneumonia* | *H. influenzae* | *H. parainfluenzae* |
| Herpes simplex virus | 47 | 6 (12.6) | 10 (21.3) | 23 (49) |
| *Rhinovirus* | 46 | 4 (8.5) | 5 (10.6) | 20 (43) |
| Influenza viruses | 37 | 5 (13.5) | 4 (10.8) 11 | (30) |
| Parainfluenzae viruses | 16 | 1 (6.3) | 2 (12.5) | 3 (19) |
| *Coronavirus* | 11 | 0 | 0 | 0 |
| Respiratory syncytial virus | 4 | 1 (25) | 0 | 2 (50) |
| Adenovirus | 3 | 0 | 0 | 1 (33) |
| *Mycoplasma pneumoniae* | 4 | 1 (25) | 2 (50) | 1 (25) |
| Total | 168 | 18 (10.7) | 23 (13.7) | 61 (36) |
| Percentage of total bacterial cultures positive | | 9.2 | 12.8 | 41.9 |

*Source*: Ref. 85.

pathogens in pulmonary infection, especially in patients with underlying chronic pulmonary disease (86). Moreover, in some geographical regions, a high rate of community-acquired legionnaires' disease has been reported. As middle-aged to elderly persons, especially those who have chronic lung disease, seem to be at greater risk for acquiring disease due to *Legionella pneumophila*, it might be advisable to include routine testing for this disease in specific cases (87).

### Nontypeable *H. influenzae*

*Arguments for a Specific Role.* Nontypeable *H. influenzae* is a common inhabitant of the normal human upper respiratory tract (88). *H. influenzae* is present in the respiratory tract of a majority of COPD patients with or without acute exacerbation (61). As underlined above (paragraph: serological studies), an antibody response to nontypable *H. influenzae* has been identified in some COPD patients with or without acute exacerbation. A study by Musher et al. (89), despite the low sample size, provides the sole argument that *H. influenzae* plays an etiological role in some exacerbations of chronic bronchitis: all six chronic bronchitis patients with acute febrile tracheobronchitis demonstrated a significant rise in opsonizing antibody to their own isolates after infection.

*Antimicrobial Susceptibility.* The incidence of ampicillin resistance reaches 15–20% of strains (90,91). Resistance is mediated by a TEM-1 type β-lactamase, which is carried by conjugative plasmids. The antimicrobial susceptibility of isolates of *H. influenzae*, established from a U.S. surveillance study by Jorgensen et al. (90), is summarized in Table 5. An alarmingly high incidence of antibiotic resistance has been recorded in other countries, particularly Spain.

### *Streptococcus pneumoniae*

*Arguments for a Specific Role.* *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia (92) and is a big cause of invasive infection in adults (93). Information about frequency and severity of pneumococcal pneumonia in patients with COPD is scant. However, *S. pneumoniae* probably plays a major role in COPD patients with pneumonia (94). In contrast to invasive pneumococcal infections, the role of *S. pneumoniae* in less fulminant illnesses in COPD patients has not been clearly established. As indicated in the epidemiological studies reported in this chapter, pneumococcus is frequently recovered from respiratory tract secretions of patients with chronic bronchitis even in the absence of signs and symptoms of infection. A reliable method for distinguishing between pneumococcal colonization and pneumococcal infection is lacking.

*Pneumococcal Vaccine.* Data regarding the potential benefit of pneumococcal vaccine in COPD patients are equivocal (9). In chronic bronchitis common pneumococcal infections are not associated with bacteremia. The usual end-point of studies evaluating the efficacy of pneumococcal vaccine is prevention of systemic pneumococcal infection. Thus, such studies do not address whether the vaccine has an effect on the nonbacteremia infections of COPD patients. All five

**Table 5** Antimicrobial Susceptibility of Bacteria Usually Recovered in COPD Patients

| | Percentage of strains susceptible to | | | | | |
|---|---|---|---|---|---|---|
| Organisms | Ampicillin | Amoxicillin clavulanic a. | Cefuroxime | Erythromycin | Tetracycline | Trimethoprim-sulfamethoxazole |
| *Haemophilus influenzae* | 83 | 100 | 100 | — | 98 | 99 |
| *Streptoccus pneumoniae* | 96/100 | 100 | 100 | 100 | 98 | 95 |
| *Branhamella catarrhalis* | 16 | 100 | 100 | 100 | <100 | 100 |

*Source*: Ref. 90.

studies assessing the efficacy of pneumococcus failed to demonstrate a clear benefit in COPD patients (95–99). In two of these studies (95,96), when COPD patients were considered like other patients at intermediate risk of pneumococcal pneumonia, a benefit from pneumococcal vaccine was seen. Moreover, a more recent study provides more precise estimates of the vaccine's efficacy against invasive pneumococcal infections in patients with illness such as chronic pulmonary, cardiac, renal disease, diabetes mellitus, or age greater than 55 years as the sole indication for receiving the vaccine (100). In this study, aggregate protective efficacy of pneumococcal vaccine given in either its 14-valent or its 23-valent form was 61% (95% confidence interval 47–72% percent; $p < 0.00001$). In the United States, the vaccine is recommended for use in all patients with COPD, considering that the benefit outweighs the risk (101).

*Antimicrobial Susceptibility.* Although most isolates of *S. pneumoniae* remain exquisitely sensitive to penicillin (MIC $\leq$ 0.06 μg/ml), relatively less susceptible strains (MIC 0.12–1.0 μg/ml) and resistant strains (MIC $\geq$ 2.0 μg/ml) have been recognized with increasing frequency throughout the world (90,102) (Table 5).

### *Branhamella catarrhalis*

*Arguments for a Specific Role. Branhamella catarrhalis* is a gram-negative coccus known to be a commensal organism in the upper respiratory tract (103). Numerous reports of infection attributable to this pathogen have been published in the last several years (104). Pulmonary infections including acute tracheobronchitis (105) and pneumonia (106) occur mainly in patients with underlying chronic pulmonary disease (107). Hager et al. (108) reviewed the published literature on *B. catarrhalis* lower respiratory tract infections before 1987 and found that 55.4% of patients had a diagnosis of COPD. Moreover, *B. catarrhalis* has been recovered from transtracheal aspirate in COPD patients with acute lower respiratory tract infections (109). Finally, Chapman et al. (110) reported that 18 of 20 COPD patients with exacerbations associated with clinical and laboratory evidence of *B. catarrhalis*, showed a specific bactericidal antibody response against their own strain following infection, suggesting that the bacterium did, in fact, cause the infection.

*Antimicrobial Susceptibility.* As many as 80–90% of *B. catarrhalis* isolates produce β-lactamase (90,111) (Table 5). The presence of β-lactamase is new and has also occurred simultaneously around the world (112). As a result, *B. catarrhalis* is considered to be resistant to ampicillin in clinical practice.

## *Clinical Findings*

The clinical circumstances in which acute exacerbations occur have not been systematically studied. In COPD, a number of conditions that worsen the chronic bronchial disease have been identified. These include an increase in cigarette

smoking, anesthesia, alcohol consumption, secretion problems secondary to decreased humidity from winter heating, and acute respiratory infections (11). The symptoms of acute bacterial exacerbations are predominantly of bronchopulmonary origin. These include increased frequency and severity of cough, increased sputum production, chest congestion and discomfort, and increased dyspnea and wheezing. Systemic symptoms may include malaise, loss of appetite, fever, and chills. The occurrence of true fever and chills or pleuritic pain suggests that pneumonia is present. However, (1) it is unusual for a patient to have all of these symptoms and (2) none of these symptoms is pathognomonic of a bacterial etiology, since other causes of exacerbations have a similar presentation. As these same findings may be present when the patient's condition is stable, their usefulness in diagnosis is limited. It is important to recognize that fever is unusual during bacterial bronchial infection and that the presence of purulent sputum is, by itself, insufficient evidence that an acute bacterial infection is present. Although there may be subtle clinical differences in the causes of acute exacerbation, including infections and noninfectious causes, there is enough similarity among different types of exacerbations to make clinical symptoms imprecise for therapeutic decision making. Several studies confirm that it is often impossible to judge clinically when an acute infection has supervened. This is particularly true of patients who always experience symptoms of cough and produce purulent sputum. Gump et al. (28), who monitored infectious episodes on the basis of change in monthly serum antibody titers for a large number of microorganisms, reported that infection could occur frequently without clinical exacerbation of bronchitis. In their study, conducted using TTA to evaluate tracheobronchial microflora in patients with stable respiratory symptoms, Irwin et al. (47) compared clinical data of the 50% of patients with tracheobronchial microflora and the 50% without identified pathogens. They were of similar age and had similar erythrocyte sedimentation rates, white blood cell counts, and pulmonary function results. Likewise, Schreiner and associates (49) demonstrated that patients with sterile TTA were clinically indistinguishable from patients with positive TTA cultures during acute exacerbations. Consequently, the subgroup of patients with infection-related exacerbation could not be clinically identified. Finally, in patients with severe acute respiratory failure requiring mechanical ventilation, Fagon et al. (56) compared the characteristics of patients with and without microorganisms isolated from protected brush specimen cultures. Results are indicated in Table 6. With the exception of fever ($38.2 \pm 0.8$ in infected patients vs. $37.7 \pm 0.6$ in noninfected patients; $p < 0.05$), clinical features were similar in the two groups.

These studies identified clinical situations that are important to recognize: (1) subclinical bacterial infection, (2) acute exacerbation due to bacterial infection, and (3) bacterial infection in patients with severe acute respiratory failure. They also demonstrated that differentiation between infected and noninfected patients cannot be observed clinically. However, the importance of determining

**Table 6** Comparison of Clinical Characteristics of COPD Patients Ventilated for Acute Respiratory Failure With and Without Infection of the Respiratory Tract

| | Results of protected brush specimen culture | |
|---|---|---|
| Clinical characteristics | Sterile ($n$ = 27) | Nonsterile ($n$ = 27) |
| Age, yr | 70 ± 10.5 | 69 ± 8.5 |
| Sex (M/F) | 20/7 | 18/9 |
| Simplified acute physiologic score | 10 ± 2 | 10 ± 3 |
| Duration of exacerbation before admission, days | 7.5 ± 7 | 6.5 ± 6 |
| Temperature °C[a] | 37.7 ± 0.6 | 38.2 ± 0.8 |
| Blood leukocytes/mm3 | 10,650 ± 3,800 | 11,760 ± 4,340 |
| Hemoglobin, g/dl | 14.7 ± 2.5 | 15.2 ± 2.8 |
| pH | 7.26 ± 0.09 | 7.30 ± 0.07 |
| HCO | 33.7 ± 6 | 32.5 ± 5 |
| $Pao_2$ ($Fio_2$: 0.21), mmHg | 41 ± 15 | 45 ± 16 |
| $Paco_2$ ($Fio_2$: 0.21), mmHg | 76 ± 24 | 66 ± 24 |
| Radiologic score | 2 ± 1 | 2.2 ± 1.2 |

[a]$p < 0.05$.
*Source*: Ref. 56.

the specific cause of acute exacerbations has major therapeutic implications. Besides the problem of the systematic use of antibiotics in COPD patients, recognition of nonbacterial causes goes beyond the selection of appropriate therapy to reverse the acute exacerbation and leads to potential changes in therapy that may influence the overall course of the disease.

### D. Pneumonia in Chronic Obstructive Pulmonary Disease

Currently, for whatever reasons, it is difficult to establish a clear picture of pneumonia in COPD, including incidence, cause, optimal diagnosis procedures, and treatment (113). However, pneumonia is usually cited to precipitate admission to hospital or to exacerbate the course of COPD patients (10,11). Conversely, chronic obstructive pulmonary diseases and other forms of chronic lung disease are cited as important predisposing conditions for community-acquired pneumonia (92). Several studies have demonstrated that COPD patients have a higher incidence of pneumococcal pneumonia than that found in other outpatient groups or the general population (114–116).

The diagnosis of pneumonia in COPD patients can be difficult. The usual clinical and laboratory criteria for diagnosing pneumonia include a new pulmonary infiltrate on the chest x-ray, cough, sputum production, fever, dyspnea, and

leukocytosis, all of which are nonspecific in the context of preexisting lung disease. Acute exacerbation with febrile tracheobronchitis can produce many of the above symptoms without radiological changes (89). There is, therefore, a significant dependence on roentgenographic findings for diagnosing pneumonia in COPD patients. Many noninfectious conditions can cause focal radiographic abnormalities and mimic bacterial pneumonia. These include pulmonary embolism, congestive heart failure with focal radiographic abnormalities, drug reaction, lung malignancy, adult respiratory distress syndrome, atelectasis, and pulmonary hemorrhage (117,118). Moreover, radiographic findings in some COPD patients provide other potential pitfalls. Bullous formation with periemphysematous infiltrates can mimic pneumonia, and large bullae suggest lung abscess or loculated empyema (119).

Consequently, it is clear that in COPD patients, careful consideration of differential diagnoses and alternative explanations of radiographic infiltrate must be considered for each patient. In spite of these difficulties, diagnosis of pneumonia is based on the analysis of the clinical, radiological, and laboratory criteria cited above. Diagnostic procedures are intended to identify the causative agents of pneumonia. The results of such diagnostic procedures must be interpreted with caution due to the usual tracheobronchial bacterial colonization in such patients. Sputum Gram stain is not intended to distinguish colonizing pathogens from infecting pathogens, nor to distinguish exacerbation of bronchitis from pneumonia. Moreover, sputum examination has not been rigorously evaluated in this particular setting (120). However, in case of pneumonia, if on a good quality Gram stain (and subsequent cultures) no gram-negative rods or staphylococci are seen, then it is likely that these organisms can be ruled out as causative pathogens. Likewise, if sputum Gram stain reveals gram-positive diplococci in a COPD patient suspected of having pneumonia, therapy must include antibiotics effective against *S. pneumoniae*.

More invasive procedures, such as bronchoscopy with PSB or bronchoalveolar lavage or transtracheal aspiration, are reasonably sensitive, specific, and safe for diagnosing bacterial pneumonia in complicated cases (121,122). However, these procedures have not been specifically tested in COPD patients, and patients requiring such invasive procedures are not clearly identified. Patients, who are severely ill on presentation, including those unable to provide specimens for analysis and in whom the diagnosis of pneumonia remains problematic, would be logical choices for more aggressive diagnostic procedures. The impact of such an approach remains to be tested in terms of cost, complication, length of stay and mortality.

In spite of the absence of precise figures for the relative frequencies of various organisms that produce pneumonia in COPD patients, it is reasonable to assume that organisms that commonly colonize the tracheobronchial tree (*S. pneumoniae*, *H. influenzae*, *B. catarrhalis*) are responsible for a large number of

pneumonia in this setting. However, multiple other pathogens could be causative. For example, Fang et al. (92) noted that COPD was the most common underlying disease in patients who had gram-negative rod pneumonia.

The true incidence of pneumonia or of any specific pathogens in COPD patients with pneumonia will probably remain unknown because of the frequent use of antibiotics in bronchitis or during acute exacerbation. This approach may be a contributing factor for a shift toward more resistant organisms colonizing the respiratory tract and producing pneumonia.

Clearly, empirical antibiotic therapy is urgently required in COPD patients with pneumonia. An adequate sputum Gram stain with a predominant organism might adequately guide initial therapy. Knowledge of the resistance levels of the principal responsible pathogens (*S. pneumoniae*, *H. influenzae*, *B. catarrhalis*) has to be taken into account in order to optimize the management of COPD patients with pneumonia.

### E. The Role of Antibiotics in Acute Exacerbation of COPD

Evaluation of the role of antibiotics in preventing and treating acute exacerbation of COPD is (1) an indirect means to evaluate the role of bacterial infection and (2) a source of knowledge to evaluate the routine use of antibiotics in clinical practice. If infection with organisms known to be sensitive to specific antibiotics plays an important role in the pathogenesis of acute exacerbation, the eradication and control of these organisms should lead to reduced morbidity and mortality.

#### *Prophylactic Use of Antibiotics*

One of the most debated questions in pulmonary medicine is whether there is any value in prophylactic administration of antibiotics to patients with chronic bronchitis (123). This controversy is important because exacerbations of bronchitis lead to workdays missed, causing great economic loss. Thus, it is worth noting that evaluation of the prophylactic use of antibiotics is based on the number of exacerbations and the number of days off work.

Eleven controlled trials of the use of antibiotics to prevent exacerbations, which included more than 25 patients, have been published since 1953 (23,124–133). Literature review of these controlled trials is summarized in Table 7. The studies involved more than 1850 patients. The antibiotics administered were tetracycline or derivatives in 10, penicillin in 5, and others in 5. The end-points were number of days off work in 1, number of exacerbations in 5, number of respiratory infections in 2, number of major exacerbations in 2, and, unfortunately, acute respiratory failure in zero. Three trials showed no difference between antibiotic and placebo groups, 3 trials showed partial advantage in subgroups of antibiotic-treated patients, and 5 trials showed a statistically significant reduction in the frequency of exacerbations in the antibiotic groups compared with those receiving placebo. Two studies (13,133) indicated that the patients who were most likely to benefit were those who suffered frequent exacerbations. It is worth noting

**Table 7** Literature Review of Controlled Trials of Prophylactic Antibiotics to Prevent Exacerbations in COPD Patients

| Authors (Ref.) | No. of patients | Antibiotics | End-point | Outcome |
|---|---|---|---|---|
| McVay and Sprunt (124) | 30 | Chlortetracycline | No. of respiratory infections | 50% decrease (NS) |
| Buchanan et al. (125) | 51 | Tetracycline | No. of major exacerbations | 0.33 vs. 1.13 exacerbation per patient ($p < 0.01$) |
| Cherniak et al. (126) | 67 | Tetracycline<br>Oleandomycin<br>Penicillin | No. of respiratory illnesses | Fewer episodes in tetracyclin group ($p < 0.01$) |
| Pridie et al. (127) | 139 | Tetracycline<br>Penicillin | No. of exacerbations | No difference |
| Francis et al. (128) | 519 | Tetracycline<br>Penicillin | Days off from work | 50% decrease ($p < 0.01$) |
| Davis et al. (23) | 29 | Tetracycline | No. of respiratory infections requiring hospitalization | No difference |
| Francis and Spicer (129) | 226 | Tetracycline<br>Penicillin | No. of attacks | No difference |
| Lepper et al. (130) | 262 | Tetracycline<br>Penicillin<br>Oleandomycin + penicillin<br>Tetracycline + erythromycine | No. of respiratory infections | Tetracycline alone: no effect<br>Tetracycline + erythromycine show significant effect |
| Fletcher and Oldham (131) | 373 | Oxytetracycline<br>Oxytetracycline + chloramphenicol<br>Oxytetracycline + sulfonamide | No. of exacerbations | Oxytetracyline alone: no effect<br>Oxytetracycline + chloramphenicol: lower no. of exacerbation in patients with more than 1 exacerbation per year |
| Pines (132) | 104 | Sulfamethoxine | No. of exacerbations | Fewer exacerbation ($p < 0.05$) |
| Johnston et al. (133) | 79 | Tetracycline | No. of exacerbations | Fewer exacerbations in patients with more than 1 exacerbation per winter ($p < 0.03$) |

that in the study conducted by Davis et al. (23), bacteriological analysis of the pretreatment and treatment period in patients receiving antibiotics compared with patients receiving placebo failed to demonstrate any differences in the identified organisms or in the total number of infections (Table 8). Moreover, this study, which used severe exacerbation requiring hospitalization as its end-point, failed to demonstrate clinical efficacy.

After a review of these conflicting results, it is readily apparent that there is, as yet, no clear-cut rationale for prophylactic treatment of infection for all patients with COPD, which suggests that bacterial infection does not play a unique pathological role in the onset of exacerbation. It seems clear that there is less rationale for long-term prophylaxis in patients without seasonal proclivity for infections, as prophylaxis in these individuals would necessitate virtually constant use of antibiotics. This practice is both costly and potentially harmful. It may in time induce the growth of highly resistant microbial strains. It seems, however, that prophylactic therapy may be of some use in highly selected patients, such as those with many exacerbations in the winter. With this in mind, the ideal drug would be cheap, free from toxic effects, effective against the whole range of bacteria responsible for acute exacerbations of COPD, and not likely to have an impact on acquired resistance. As none of the licensed antibiotics fulfills these conditions, regular changes in prophylactic regimens should be advocated.

**Table 8** Incidence of Common Sputum Organisms and Total Number of Infections During Chemoprophylaxis Treatment of Pulmonary Emphysema

| Organisms | Patients receiving placebo ($n$ = 13), $n$ (%) | Patients receiving tetracycline ($n$ = 16), $n$ (%) |
|---|---|---|
| Pretreatment period | | |
| *H. influenzae* | 8 (61.5) | 13 (81.3) |
| *S. pneumoniae* | 3 (22.1) | 2 (12.5) |
| *S. aureus* | 4 (30.8) | 7 (43.8) |
| Gram-negative rods | 6 (46.2) | 8 (50.0) |
| Treatment period | | |
| *H. influenzae* | 12 (92.3) | 14 (87.5) |
| *S. pneumoniae* | 12 (92.3) | 7 (43.8) |
| *S. aureus* | 13 (100) | 16 (100) |
| Gram-negative rods | 12 (92.3) | 16 (100) |
| Total number of infections | 35 | 29 |
| Percentage of patients with infection | 77% | 75% |

*Source*: Ref. 23.

### *Curative Use of Antibiotics*

The role of short-term use of antibiotics in acute exacerbation of COPD is also difficult to assess. Most studies compare various antimicrobial agents or evaluate the effect of an antibiotic on the natural history of an acute exacerbation. None of them include untreated controls. From these studies, one cannot specify the exact role of antibiotics in this setting or identify the patients from whom an effect can be expected (2,5,10,134–136). Only eight trials determine the value of antibiotics in acute exacerbation of COPD (24,137–143). These prospective placebo-controlled randomized studies are shown in Table 9. Once again, the results of these studies should be interpreted with caution because of heterogeneous patient populations and various flaws in study design. The six oldest studies, except for one (141), are clearly inconclusive in showing a beneficial effect from antibiotics. Two more recent and well-conducted studies have looked again at the value of antibiotic treatment (Table 10).

Nicotra et al. in 1982 (143) studied 40 patients with enough symptoms to require hospitalization, but with no evidence of pneumonia, fever or leukocytosis. In addition to bronchodilators and steroid therapy, patients were randomly treated with either tetracycline or a placebo. Follow-up found no significant differences in

**Table 9** Literature Review of Controlled Trials of Antibiotics to Treat Acute Exacerbation of COPD

| Authors (Ref.) | No. of patients | No. of exacerbations | Antibiotics | Results |
|---|---|---|---|---|
| Elmes et al. (137) | 88 | 146 | Oxytetracycline | No difference |
| Berry et al. (138) | 53 | 53 | Oxytetracycline | No difference |
| Elmes et al. (139) | 56 | 56 | Ampicillin | No difference |
| Petersen et al. (140) | 43 | 43 | Chloramphenicol | No difference |
| Pines et al. (141) | 30 | 30 | Penicillin and streptomycin | Treated group recovered more promptly |
| Pines et al. (142) | 259 | 259 | Tetracycline or chloramphenicol | Treated group recovered more promptly<br>No difference by one month |
| Nicotra et al. (143) | 40 | 40 | Tetracycline | No difference |
| Anthonisen et al. (24) | 173 | 362 | Trimethoprim-sulfa or aminoxillin or doxycycline | Earlier resolution and prevention of deterioration in the treated group |

**Table 10** Analysis of Two Studies Evaluating the Value of Antibiotics in Acute Exacerbations of COPD

| | Study 1[a] | | | | | Study 2[b] | | |
|---|---|---|---|---|---|---|---|---|
| No. of patients | 40 | | | | | 173 | | |
| No. of exacerbations | 40 | | | | | 362 | | |
| Inclusion criteria | Exacerbation requiring hospitalization | | | | | Exacerbation with 3 subgroups of severity defined in terms of symptoms | | |
| Exclusion criteria | Pneumonia, fever, leukocytosis | | | | | Cancer, stroke, left ventricular failure, other infectious disease requiring antibiotics | | |
| Associated therapeutics | Bronchodilators and glycocorticoids | | | | | Bronchodilators and glycocorticoids | | |
| Treatment | Tetracycline 500 mg 4 times daily, for 7 days | | | | | Trimethoprim-sulfamethoxazole (160/800 mg twice daily) or amoxicillin: 250 mg four times daily or doxycycline: 100 mg daily | | |
| Major end-points | $PaO_2$ and $FEV_1$ after 7 days | | | | | Resolution of symptoms and/or deterioration of symptoms within 21 days | | |
| Results | Antibiotic group $n = 20$ | | | Placebo group $n = 20$ | | Antibiotic group $n = 182$ | | Placebo group $n = 180$ |
| | day 1 | day 7 | | day 1 | day 7 | | | |
| $PaO_2$ | 58.3 | 74.1 | NS | 60.3 | 68.1 | Success* | 68% | 55% |
| $FEV_1$ | 0.88 | 1.02 | NS | 0.92 | 1.08 | Deterioration** | 9.9% | 18.9% |

*$p < 0.01$; **$p < 0.05$.
[a]From Ref. 143.
[b]From Ref. 24.

pulmonary function measurements ($FEV_1$), arterial blood gases, bacteriology, or symptoms.

In 1987, Anthonisen et al. (24) completed a study of 173 outpatients who had been followed for an average of 3.5 years. They treated a total of 362 acute exacerbations. They found that antibiotic-treated episodes were significantly more likely to be resolved within 21 days than placebo-treated ones and significantly less likely to be associated with clinically alarming deterioration after the first 72 hours. This conclusion was supported by the more rapid recovery of peak flow in patients with antibiotic-treated exacerbations. However, the authors themselves stated that the 13% difference in success rate "does not appear to be a great clinical advantage" in such patients with "soft" definition of onset and resolution of exacerbations. Although failures were uncommon in this study, they suggested that the difference in failures with deterioration was probably of greater clinical significance because of the inherent need for additional treatment, increased cost, and increased morbidity. The analysis performed by Anthonisen et al. of the outcome of exacerbations in patients with three different degrees of severity indicated that the success rate was significantly greater in the most severe exacerbations treated with antibiotics (62.9% vs. 43.0% in the placebo group). Moreover, deterioration was more than twice as common with placebos (22% of patients) as with antibiotics (10% of patients) in this group. Accordingly, the authors of this milestone study concluded that patients with the "most severe" exacerbations, presenting with increased dyspnea, increased sputum, and sputum purulence, should be treated with antibiotics as long as they were known to tolerate the proposed antibiotic.

However, reviewing all of these controlled studies, one finds not only a lack of uniform response to antibiotics, but also a rather marginal clinical response to their use, even when a statistical advantage is clearly shown.

None of them evaluated the value of antibiotic treatment on the management of COPD patients during acute respiratory failure. In the study conducted by Fagon et al. (56) in COPD patients ventilated for ARF, with evaluation of the distal bronchial microflora using a protected specimen brush, a small subgroup of patients with sterile PSB cultures were not treated with antibiotics. In comparisons of patients with negative culture and not treated with antibiotics, patients with negative culture treated with antibiotics, and patients with positive culture treated with antibiotics, mortality rate (11, 11, and 11%, respectively), duration of mechanical ventilation ($7.4 \pm 5.2$, $6.4 \pm 2.1$, and $10 \pm 4.8$ days, respectively), and duration of stay in the ICU ($10.6 \pm 7.3$, $9.2 \pm 3.0$, and $13 \pm 5.5$ days, respectively) were similar.

Finally, antibiotic therapy would be more attractive if we were able to identify exacerbation types that are associated with major differences between antibiotic and placebo therapy and patient types who would benefit from antibiotic treatment. Unfortunately, there are no clear data available for making this distinction, and this particular clinical problem is clearly an area for future investigation.

Comprehensive care for patients with acute respiratory failure in COPD is made up of many individual therapeutic modalities, of which some are established through rigorous scientific investigation and others are based upon clinical judgment and experience. As it is impossible to identify a cause with certainty in most cases, each patient should be treated individually. Since at least 50% of patients with acute exacerbation and/or acute respiratory failure (1) fail to show any evidence of infection when accurate sampling procedures such as transtracheal aspiration or protected specimen brush are used and (2) respond to placebos, some restraint should be exercised and the role of antibiotics in the management of such patients be reassessed. The current concern over the rational use of antibiotics, their contribution to nosocomial infection, and selection of resistant bacteria and the economic burden that unnecessary use may represent requires that this reassessment be carried out. Although controversy about possible microbial pathogenesis and the value of antibiotics persists, most clinicians elect to treat acute exacerbations as infectious events and direct therapy at *S. pneumoniae*, *H. influenzae*, and, more recently, at *B. catarrhalis*.

## II. Ventilator-Associated Pneumonia

Nosocomial bacterial pneumonia is one of the three most common hospital-acquired infections, and pneumonia is the leading cause of death from nosocomial infection in all countries. Hospital-acquired pneumonia occurs at a frequency of 0.6–1.0 episode per 100 hospitalizations and in 18% of postoperative patients (17,144). Intubated patients may have rates of pneumonia 7–21 times higher than patients without a respiratory therapy device (145).

In spite of the development of non-invasive ventilation (14,146) in acute exacerbation of COPD, conventional techniques of ventilation administered via endotracheal tubes remain standard therapy for acute respiratory failure when conservative management fails to improve the patient's condition or when the situation seems desperate prior to any treatment. Consequently, COPD patients are among the most frequent populations admitted to the ICU and ARF in COPD patients is one of the most frequent causes of intubation and ventilation in ICU patients.

However, characteristics of ventilator-associated pneumonia in COPD patients are difficult to assess. Epidemiological studies of ventilator-associated pneumonia were conducted either in a general population of ICU patients or in surgical patients, or were limited to certain microbial etiologies, but none were focused on COPD patients. There is, moreover, no evidence that epidemiological characteristics of ventilator-associated pneumonia in COPD patients are different from pneumonia acquired by other ICU patients. Consequently, the data reported here are based mainly upon studies conducted in the ICU population including COPD and other types of critically ill patients.

### A. Incidence

The majority of studies have reported varying rates of nosocomial pneumonia of between 8 and 20% (147–151). This risk is higher in the subset of ICU-intubated patients receiving mechanical ventilation; for instance, in the study conducted by Cross and Roup (152), which included 13,068 patients, pneumonia rates increased 10-fold when patients were intubated and mechanically ventilated.

In ventilated patients, rates of nosocomial pneumonia range from 9 to 41% in the majority of studies (147–151). Langer et al. (153) found in their study, which included 724 critically ill patients who had been ventilated for at least 24 hours, a mean rate of 23% of nosocomial pneumonia. The incidence rose from 5% in patients receiving ventilation for one day to 69% in patients who were ventilated for more than 30 days. Fagon et al., using protected specimen brush for diagnosing ventilator-associated pneumonia, found a rate of 9% (147). Using an actuarial method, the cumulative risk of pneumonia was estimated to be 6.5% at 10 days and 19% at 20 days after the onset of mechanical ventilation. The incremental risk of pneumonia was constant with a mean of about 1% per day.

There are no data specifying the incidence of ventilator-associated pneumonia in COPD patients hospitalized in an ICU for acute respiratory failure. In the study conducted by Fagon et al. (147) in 567 ventilated patients, 128 had preexisting COPD. The incidence of nosocomial pneumonia was 7.8% in COPD patients, which was not significantly different from the entire population (9%). Although the incidence of nosocomial pneumonia has not been evaluated during ventilation via nasal or facial mask, the high risk of pneumonia associated with endotracheal intubation is an important argument for the development of noninvasive ventilation. Moreover, because the risk of nosocomial pneumonia in ventilated patients is a time-related risk throughout the entire ventilation period, reduction of the duration of mechanical ventilation must be the objective in COPD patients ventilated for ARF.

### B. Mortality and Morbidity

Crude mortality rates of 30–76% have been reported for nosocomial pneumonia in ventilator-dependent patients (147–151). Despite variations between studies, the risk of death for ventilated patients with nosocomial pneumonia seems to be higher than for nonventilated patients, exceeding 50% in the majority of reports.

There is little doubt that critically ill patients who develop nosocomial pneumonia have an increased mortality rate compared to other ICU patients (148,150). The question is to determine if nosocomial pneumonia actually causes increased mortality or if nosocomial pneumonia is present in critically ill patients who die. Two factors make this important question difficult to resolve. First, numerous studies have demonstrated that severe underlying disease predisposes patients to developing pneumonia (148,151,154,155). Mortality rates are high in

such patients for many reasons, and it is difficult to establish whether such critically ill patients would have survived if nosocomial pneumonia had not occurred. The second factor is the difficulty of establishing a firm diagnosis of pneumonia in ventilated patients. As indicated in Section II.F, several studies have shown that many patients diagnosed as having pneumonia on the basis of commonly used clinical criteria do not, in fact, have pneumonia. Thus, the widely diverging figures reported for the incidence and mortality rates from nosocomial pneumonia may reflect not only differences in the patient population studied, but also differences in the diagnostic criteria used. Three matched cohort studies (156–158) of nosocomial pneumonia, in which subjects were compared according to demographic factors and underlying disease, suggested that the relative risk of pneumonia in inducing death was between 1.5 and 3.6. Using strict criteria for identifying patients with ventilator-associated pneumonia, Fagon et al. reported that mortality attributable to nosocomial pneumonia exceeded 25% and that in cases of pneumonia due to *Pseudomonas* spp. or *Acinetobacter* spp., mortality exceeded 40% (158). This result confirms the relationship between etiological agents and mortality from nosocomial pneumonia. The prognosis associated with aerobic gram-negative bacillary pneumonia is considerably worse than that with gram-positive agents (18,159).

In spite of the results observed by Burrows and Earle in 1969 (31) indicating that more than 20% of COPD patients died with infection present (but the precise diagnosis of infection was not specified in this study), no data suggest that the prognosis of nosocomial pneumonia is worse in COPD patients than in other ICU patients. On the contrary, in the study conducted by Torres et al. (151), the presence of preexisting COPD in patients with nosocomial pneumonia was not significantly associated with a worse outcome in either the univariate or the multivariate analysis.

It is impossible to estimate accurately the morbidity and excess costs associated with nosocomial pneumonia. However, with respect to morbidity measures, excess stay in hospital, as a direct consequence of pneumonia, has been estimated to be in the 6- to 9-day range (156–158). This prolonged hospital stay underscores the considerable financial burden imposed by the development of nosocomial pneumonia. The average excess cost for nosocomial pneumonia was estimated at $1,255 in 1982 (160) and $2,863 in 1985 (161).

### C. Etiological Agents

The importance of gram-negative bacilli as pathogens in nosocomial respiratory infection has been repeatedly documented (147,162–165). Table 11 shows the bacteriological results of two large studies conducted in patients with ventilator-associated pneumonia in whom analyses were restricted to uncontaminated specimens (147,165). The predominant organisms were *P. aeruginosa*, *Acinetobacter*

**Table 11** Organisms Recovered from Protected Brush Specimens and Bronchoalveolar Lavage in Ventilator-Associated Pneumonia

| | Study 1[a] | Study 2[a] |
|---|---|---|
| No. of episodes of pneumonia | 52 | 25 |
| Technique | PSB | PSB+BAL |
| Threshold count (cfu/ml) | $10^3$ | $10^3$ |
| Gram-negative bacteria | No. (%)[c] | No. (%)[c] |
| *P. aeruginosa* | 16 (31) | 7 (28) |
| *Acinetobacter* spp. | 8 (15) | 6 (24) |
| *Proteus* spp. | 8 (15) | 0 |
| *M. catarrhalis* | 5 (10) | 0 |
| *Haemophilus* spp. | 5 (10) | 0 |
| *E. coli* | 4 (8) | 3 (12) |
| *Klebsiella* spp. | 2 (4) | 3 (12) |
| *E. cloacae* | 1 (2) | 1 (4) |
| *P. maltophila* | 0 | 0 |
| *Legionella* spp. | 1 (2) | 2 (8) |
| Miscellaneous | 1 (2) | 1 (4) |
| Gram-positive bacteria | | |
| *S. aureus* | 17 (33) | 5 (20) |
| *S. pneumoniae* | 3 (6) | 1 (4) |
| Other Streptococci | 8 (15) | 4 (16) |
| *Corynebacteria* spp. | 4 (8) | 0 |
| *S. epidermidis* | 0 | 1 (4) |
| Anaerobes | 1 (2) | 1 (4) |
| Polymicrobial flora | 21 (40) | 10 (40) |

*cfu: Colony-forming units.
[a]From Ref. 147.
[b]From Ref. 165.
[c]Sum of percentages exceeds 100% owing to polymicrobial flora.

spp., and *Proteus* spp. A relatively high rate of gram-positive pneumonia was also reported in these studies, with *S. aureus* involved in 33 and 20% of cases, respectively. Moreover, it is worth mentioning that in one third of the analyzed pneumonias, organisms such as streptococci other than *S. pneumoniae*, *Corynebacterium* spp., and *Haemophilus* spp. were recovered, mostly as part of a polymicrobial flora. The latter organism seems to be nosocomially acquired more frequently in COPD patients (167). Recently, the high rate of polymicrobial infection in nosocomial pneumonia has been underlined by several authors with rates varying between 13 and 40% of all pneumonias (148,163).

### D. Predisposing Factors

A number of factors that increase the risk of pneumonia in the hospital setting have been suspected or identified. Only a few studies of potential risk factors have utilized accurate statistical models to define independent risk determinants. The role of prehospitalization risk factors, such as the presence of preexisting chronic obstructive pulmonary disease, was not examined in detail in any of these studies. Seven studies have examined risk factors in the development of pneumonia in different groups of hospitalized patients: in the postoperative period (154), in the elderly (167), in nonneutropenic adult patients admitted to a 1000-bed teaching hospital (155), in ICU patients (168), in ventilated patients (148,151), or in cases of nosocomial pneumonia due to *S. aureus* (169). In the study conducted in patients during the postoperative period, Garibaldi et al. stated that acquisition of pneumonia was closely associated with preoperative markers of the severity of underlying disease, history of smoking or COPD, longer surgical procedures, longer preoperative stays, and thoracic or upper abdominal interventions (154). The results of multivariate analyses performed in the other six studies are summarized in Table 12. These data indicated specific high-risk populations (patients with COPD, comatose patients, postoperative patients, particularly following thoracoabdominal surgery, and ARDS patients) and specific treatment management (intubation, reintubation, frequent changes of ventilator circuits, nasogastric tube, bronchoscopy, use of $H_2$-blockers, and use of glycocorticoids) as being independently associated with nosocomial pneumonia.

The use of antibiotics in the hospital setting has been associated with increased risk of nosocomial pneumonia (32,164,170). These so-called superinfections presumably occur as a consequence of selection of more resistant bacterial pathogens during treatment of a primary infection. In one report, 149 patients treated in hospital with penicillin or erythromycin for community-acquired pneumonia experienced a 16% incidence of pulmonary superinfection (32). In another study conducted in ventilated patients, 65% of the pneumonias among patients receiving broad-spectrum antibiotics, but only 19% of pneumonias among patients not having received prior treatment with antibiotics, included *Pseudomonas* or *Acinetobacter* spp. as the responsible organisms (147). Thus,

1. COPD patients are clearly identified as a population at high risk for the development of nosocomial pneumonia in three of the four studies specifically evaluating this underlying condition (154,155,165).
2. Intubation and mechanical ventilation are identified as procedures at risk for causing the development of nosocomial pneumonia.
3. Previous use of antibiotics is clearly identified as treatment at risk for causing the development of nosocomial pneumonia—at least those due to multiresistant organisms.

**Table 12** Factors Selected by Multivariate Analysis Associated with a High Risk of Acquiring Nosocomial Pneumonia

| Risk factors | Relative or crude odds ratio | 95% confidence interval | *p*-value |
|---|---|---|---|
| Nonneutropenic adults[a] | | | |
| COPD | 3.7 | 2.6–5.3 | 0.0003 |
| Depressed consciousness | 5.8 | 3.6–9.3 | 0.0002 |
| Intubation | 6.7 | 4.1–10.9 | 0.0001 |
| Gastric aspiration | 10.6 | 4.8–23.1 | 0.003 |
| Thoracoabdominal surgery | 4.7 | 2.9–7.5 | 0.0018 |
| Age (>70 yr) | 2.3 | 1.5–3.3 | 0.04 |
| Elderly (>65 yr)[b] | | | |
| Albumin ≤3.0 g/dl | 14.7 | 4.0–54.8 | 0.0001 |
| Neuromuscular disease | 24.8 | 1.6–381.5 | 0.02 |
| Intubation | 5.2 | 1.1–25.6 | 0.04 |
| *Staphylococcus aureus* pneumonia[c] | | | |
| Coma | ND | ND | 0.004 |
| ICU patients[d] | | | |
| Nasogastric tube | 6.48 | 2.12–19.82 | 0.0008 |
| Thoracoabdominal surgery | 4.34 | 1.43–13.14 | 0.008 |
| Recent bronchoscopy | 2.95 | 1.02–8.52 | 0.04 |
| Ventilated patients[e] | | | |
| Intracranial pressure monitoring | 4.2 | 1.7–10.5 | 0.002 |
| Cimetidine | 2.5 | 1.2–5.0 | 0.01 |
| 24-hr circuit changes | 2.3 | 1.2–4.7 | 0.02 |
| Fall-winter season | 2.1 | 1.1–4.2 | 0.04 |
| Ventilated patients[f] | | | |
| Reintubation (>1) | 5.0 | 3.5–7.0 | 0.00001 |
| Gastric aspiration | 5.05 | 3.35–7.8 | 0.0002 |
| MV duration (>3 days) | 1.17 | 1.15–1.19 | 0.015 |
| COPD | 1.89 | 1.38–2.59 | 0.048 |
| Use of PEEP | 1.85 | 1.30–2.64 | 0.092 |

MV: mechanical ventilation; COPD: chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure.

[a]From Ref. 155.

[b]From Ref. 167.

[c]From Ref. 169.

[d]From Ref. 168.

[e]From Ref. 148.

[f]From Ref. 151.

4. Nosocomial pneumonias are more often due to *Pseudomonas* spp. or *Acinetobacter* spp. in case of prior antibiotic treatment and are then associated with high mortality rate.

### E. Pathogenesis

Pneumonia results from microbial invasion of the normally sterile lower respiratory tract caused by either a defect in host defenses, challenge by a particularly virulent microorganism, or an overwhelming inoculum. Although hospital-acquired pneumonias may occur as metastatic infections secondary to bacteremia, the infrequent association of nosocomial pneumonia with bacteremia suggests that the majority of nosocomial pneumonia results from aspiration of potential pathogens that have colonized the mucosal surfaces of the upper airways (171). In the study by Johanson et al. (171), 45% of the 213 patients admitted to a medical ICU became colonized with aerobic gram-negative bacilli by the end of their first week in hospital. Of these 95 colonized patients, 22 (23%) developed subsequent nosocomial pneumonia. By comparison, only 4 of the 118 noncolonized patients (3.4%) developed pneumonia. Moreover, the risk of airway colonization increased as a function of time in the hospital. Risk factors for upper airway colonization with gram-negative bacilli appear to be more advanced degrees of illness, longer hospitalization, prior or concomitant use of antibiotics, intubation, azotemia, and underlying pulmonary disease including COPD (170–172).

Colonization of the respiratory epithelium in hospitalized patients is related to an increased affinity for the attachment of gram-negative bacilli (173), particularly in patients with chronic tracheostomy (174). Also, considerable data have been collected suggesting that mucosal cell surface glycoproteins, including fibronectin, play in integral part in modulating oropharyngeal bacterial ecology (175).

Interpretation of the data concerning colonization and pneumonia suggests that colonization of the oropharynx is a marker for critically ill patients who have multiple deficiencies in the host-defense system of their respiratory tract. Thus, the patient whose oropharynx is colonized by gram-negative bacteria is also likely to have other impairments in his or her cellular and humoral responses to bacterial invasion of the lungs. These defects predispose patients to the development of pneumonia.

The source of organisms colonizing the upper airway has been extensively studied during the past decade. Studies of nosocomial infection have demonstrated an association between infection with a particular organism and the presence of the same organisms in the intestine (176). In a study of daily cultures from rectal, hypopharyngeal, and tracheal sites, Schwartz et al. showed that Enterobacteriaceae were commonly cultured from the hypopharynx and rectum before their appearance in tracheal culture, which suggests that patients may become colo-

nized by endogenous flora (176). It is usually accepted that the most common vector for transmission of environmental flora is the hands of health-care personnel (177).

Recent data suggest that the use of gastric alkalinization to prevent stress ulcers and bleeding in hospitalized patients is producing larger numbers of patients with extensive bacterial overgrowth in the upper gastrointestinal tract. Reduced gastric acid in intubated patients may result from the intrinsic decrease in gastric acid production, for example, in elderly patients, with malnutrition, achlorhydria, or gastrointestinal diseases (178), or from the use of antacids or histamine type 2 blockers, which neutralize or block gastric acid secretion (18,179). Several randomized studies have examined pneumonia rates in mechanically ventilated patients given different types of stress ulcer prophylaxis. The results are summarized in Table 13 (149,180–185). Three studies have demonstrated lower rates of pneumonia in patients randomized to receive sucralfate compared to antacids with or without cimetidine (149,183,184). Increased pH due to tube feeding may also increase gastrointestinal colonization by gram-negative bacilli. Pingleton et al. (186) demonstrated gastric colonization in 100% of 18 ventilated patients receiving enteral feeding, and 63% of them subsequently developed nosocomial pneumonia. Considering the supposed pathophysiology, it seems clear that the effect of the drugs on the gastric pH is the principal mechanism leading to an increase in pulmonary infections (187).

Figure 1 represents a number of factors that have been suspected or identi-

**Table 13** Frequency of Ventilator-Associated Nosocomial Pneumonia in Prospective Studies Comparing Conventional Bleeding Prophylaxis with Antacids and/or $H_2$-Antagonists vs. Control Groups Without Medication to After Gastric pH (Placebo or No Treatment, Pirenzepine, Sucralfate)

| | | Frequency of nosocomial pneumonia | |
|---|---|---|---|
| Authors (Ref.) | No. of patients | Control, Pirenzepine, or Sucralfate (%) | Antacids/$H_2$-Antagonists (%) |
| Cheadle et al. (180) | 200 | 3[a] | 13 (cimetidine) |
| Reusser et al. (181) | 40 | 38[a] | 37 (ranitidine) |
| Tryba (182) | 61 | 9[b] | 29 (ranitidine) |
| Driks et al. (149) | 130 | 12[c] | 23 (antacids ± $H_2$-antagonists) |
| Tryba (183) | 61 | 10[c] | 34 (antacids) |
| Kappstein et al. (184) | 104 | 26[c] | 45 (cimetidine) |
| Mahul et al. (185) | 145 | 18[c] | 24 (antacids) |

[a]Control.
[b]Pirenzepine.
[c]Sucralfate.

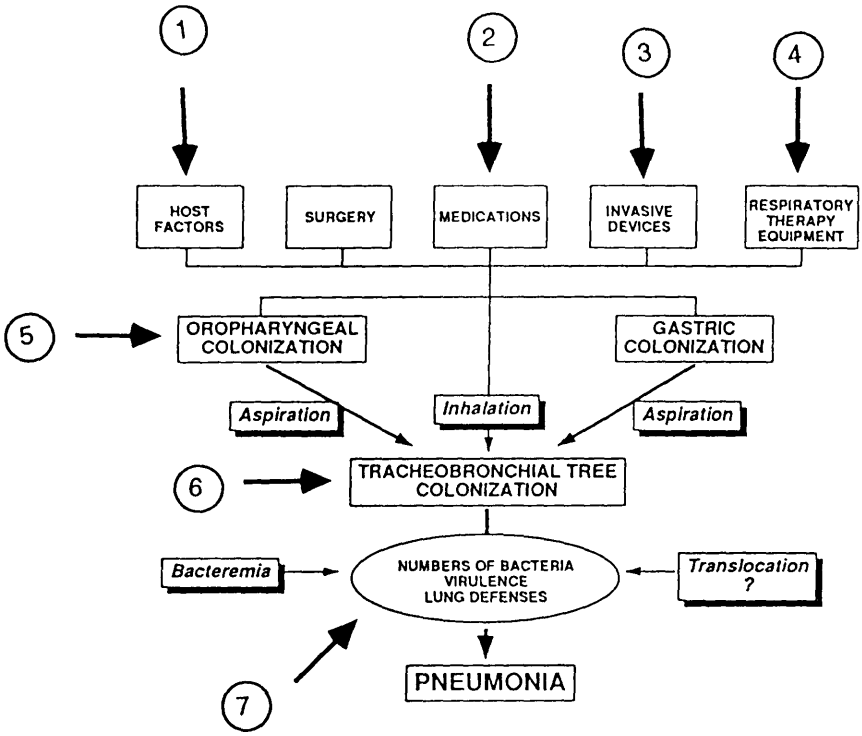


**Figure 1** Risk factors for colonization with nosocomial pathogens, mechanisms for microorganisms to enter the lower respiratory tract, and pulmonary host defenses against infection. Arrow indicates potential influence of preexisting COPD. (1) Preexisting chronic lung disease, age, nutritional status; (2) corticosteroids, antibiotics, antacids, $H_2$ blockers; (3) intubation, tracheostomy; (4) ventilator circuit; (5) preexisting chronic lung disease; (6) preexisting colonization of the tracheobronchial tree; (7) preexisting chronic lung disease. (From Ref. 18.)

fied as increasing the risk of pneumonia. Potential influences of preexisting COPD are indicated. At almost each step of the process leading to nosocomial pneumonia, previous chronic obstructive pulmonary disease could be an influence.

### F. Diagnosis

It is as difficult to determine if nosocomial pneumonia has developed in COPD patient ventilated for ARF as in other ventilated patients.

### *Clinical Diagnosis*

The classical clinical findings for pneumonia, such as fever, pulmonary infiltrate, sputum production and elevated leukocyte count, may not be present in the ICU patient with nosocomial pneumonia. Alternatively, these findings may be present, but not caused by pneumonia. Most critically ill patients, including COPD patients, have serious underlying conditions, increased oropharyngeal colonization, and numerous reasons for elevated body temperature and leukocytosis. Furthermore, chest radiographic changes may be caused by pulmonary edema, pulmonary infection, or atelectasis or modified by preexisting lung disease.

Therefore, results of studies evaluating the usefulness of clinical parameters in identifying ventilated patients with nosocomial pneumonia have generally been disappointing. Andrews et al. (188) found that clinical diagnoses were erroneous in 29% of the 24 acute respiratory distress syndrome patients who died when they compared clinical criteria with histological findings. The following clinical criteria were present in the groups with and without pneumonia, respectively: fever, 100% versus 80%; leukocytosis or leukopenia, 100% versus 80%; pathogens in the sputum, 86% versus 70%; and asymmetric infiltrate on chest films, 57% versus 30%. In a similar study conducted by Bell et al. (189), 38% of the 35 ARDS patients with pneumonia were also misdiagnosed. Likewise, in the study conducted by Fagon et al. in 147 ventilated patients, 16 clinical variables such as fever, leukocytosis, hypoxemia, or radiological findings were evaluated by stepwise logistic regression analysis, but no combinations were found that were useful in distinguishing between patients with and without bacterial pneumonia (190). The same authors (191), in a prospective study evaluating clinical judgment for the diagnosis of pneumonia, found that an accurate diagnosis was made in 77% of cases and that therapeutic plans were appropriate in only 64% of cases.

Consequently, unless further evaluation is undertaken, most patients with fever and pulmonary infiltrates are treated with one or more antibiotics. This policy, based only on clinical evaluation and the results of cultures of tracheal aspirates, has several potential disadvantages. A large number of patients without nosocomial pneumonia are treated with antibiotics, which exposes them to unnecessary toxicity, delays the diagnosis of the true etiology of fever and pulmonary infiltrate, and increases hospital costs.

### *Examination of Tracheal Secretions*

This procedure remains a mainstay in the evaluation of pneumonia, yet numerous studies have demonstrated discrepancies between culture results obtained from these secretions and the actual pathogens causing disease of the respiratory tract. Analyses of cultured tracheal aspirate specimens show moderate-to-high sensitivity (varying from 58 to 100%) but a generally low specificity (varying from 0 to 59%) (165,192–199). These results are not surprising, since the respiratory tract

of most ventilated patients is colonized with potential pulmonary pathogens whether or not deep pulmonary infection is present. As indicated above, in COPD patients, since hospital-acquired colonization occurs in a previously colonized respiratory tract, interpretation of the results of cultures of tracheal secretions is even more difficult, and such a bacteriological technique is inaccurate for diagnosing nosocomial pneumonia. For these reasons, a number of specialized microbiological assays and several invasive techniques for obtaining specimens have been described as being potentially useful for improving diagnostic specificity for nosocomial pneumonia.

### *Bronchoscopic Specimens*

Bronchoscopy allows direct access to the lower airways for sampling bronchial and parenchymal tissues. However, the bronchoscope has to traverse the endotracheal tube and proximal airways where contamination is likely to occur. Fiber optic bronchoscopy (FOB) is generally regarded as safe. The risk inherent in such an examination appears to be slight, even in critically ill patients needing mechanical ventilation, although the associated occurrence of cardiac arrhythmias, hypoxemia, or bronchospasm is not unusual (200,201). In patients with a history of COPD and/or smoking, FOB not only aids the diagnosis of nosocomial pneumonia, but also enables careful examination of the tracheobronchial tree. Two main techniques have been suggested as being of value in establishing a specific diagnosis of pneumonia in critically ill patients.

#### The Protected Specimen Brush Technique

This method is in fact based on the combination of four different techniques: (1) the use of fiberoptic bronchoscopy to directly sample the site of inflammation in the lung; (2) a special double lumen–catheter brush system with a distal occluding plug to reduce contamination of lower airway aspirate by flora colonizing proximal airways; (3) a brush to calibrate the volume of respiratory secretions obtained; and (4) a quantitative culture technique to aid in distinguishing between airway colonization and serious underlying infection, with the cut-off threshold between the two set at $10^3$ cfu/ml. To obtain meaningful results with the PSB technique, it is very important to follow a precise methodology, including (1) not injecting lidocaïne through the suction channel of the FOB and avoidance of suction of upper airway secretions, (2) the proper positioning of the FOB close to the orifice of the bronchus draining the subsegment with new infiltrate on the chest radiograph, and (3) after collection, immediate placement of the brush into 1 ml of saline or Ringer's solution to avoid drying and rapid loss of bacteria and immediate transport to the laboratory for culture.

The usefulness of the PSB technique in evaluating patients receiving mechanical ventilation who are suspected of having pneumonia has been extensively investigated in both animal and human studies (190,202–213). In the four studies

comparing the accuracy of the PSB method with an acceptable "gold" standard (202–205), sensitivity of the PSB technique was high, ranging between 80 and 100%, and the rate of false-positive results was quite low. Despite the need for interpretive caution, clinical studies (206–213) indicate that the PSB technique offers a rather sensitive and specific approach in critically ill patients to establish the organisms in case of pneumonia and to differentiate between colonization of the upper respiratory tract and distal lung infection. Pooling the results of the 18 studies evaluating the PSB technique in a total of 524 critically ill patients showed the overall accuracy of this technique for diagnosing nosocomial infection to be high, with a sensitivity of 89% (95% CI, 86.9–92.9%) and a specificity of 94.3% (95% CI, 91.8–96.8%) (214).

One important modification has recently been suggested with apparently acceptable results. With the aim of simplifying the procedure and reducing costs, Pham et al. (212) evaluated a new device composed of a plugged telescoping catheter (PTC) in 55 patients. The authors found that this device gave similar results to PSB technique in 74% of cases. Furthermore, they indicated that blind or directed PTC samples had similar concordance with PSB samples taken via bronchoscopy. Before extensive clinical use of the PSB technique, some potential limits or drawbacks of this method have to be considered, including interpretation in patients with diffuse lung injury and in patients receiving prior antimicrobial therapy, risks inherent in bronchoscopy, cost, and the time needed for culture results (24–48 hr), which means that information to guide initial antimicrobial therapy is not available.

### The Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) has been extremely helpful in diagnosing a wide range of lung infections in immunocompromised persons. This technique obtains samples from a relatively large area of the lung, and the cells and liquid recovered can be examined under microscope immediately after the procedure and are also suitable for culture using quantitative techniques.

In COPD patients, because of the chronic obstruction of the airways and majoration of the inflammation of bronchial mucosa during acute exacerbation, aspiration of the sterile physiological solution is often difficult during bronchoalveolar lavage. In such patients, (1) sedatives associated with a short-acting paralytic agent are recommended, (2) more than 140 ml are frequently needed to retrieve secretions from the periphery of the lung subsegment, and (3) microscopic analysis of BAL must include the analysis of columnar epithelial cells that are indicators of tracheobronchial proximal sampling.

At least four studies have investigated the value of BAL fluid quantitative culture for diagnosing nosocomial pneumonia in ventilated patients (165,192,209, 215) with diverging results. Johanson et al., in an animal study using a quantitative culture of BAL to predict the absence of presence of pneumonia (204), indicated

that approximately 30% of the patients without pneumonia would have been treated and 40% of patients with pneumonia would not have been treated.

Two new techniques were suggested to circumvent the problem of BAL fluid contamination by the flora present in proximal airways. The first was described by Rouby et al. (216) and is based on the use of a plugged double catheter blindly wedged into the distal airways to perform a small lavage with 20 ml of saline solution. The second was described by Meduri et al. (213) and is based on a protected transbronchoscopic balloon-tipped catheter designed to avoid exposing the instilled and aspirated BAL solution to contaminants. The authors reported promising results, suggesting that these techniques merit further evaluation.

Microscopic evaluation of cytocentrifuged preparations obtained easily and rapidly from BAL fluid enables detection of the presence or absence of intracellular or extracellular bacteria in the cells and secretion lining the lower respiratory tract (Fig. 2). Chastre et al. (209) have evaluated the usefulness of this type of

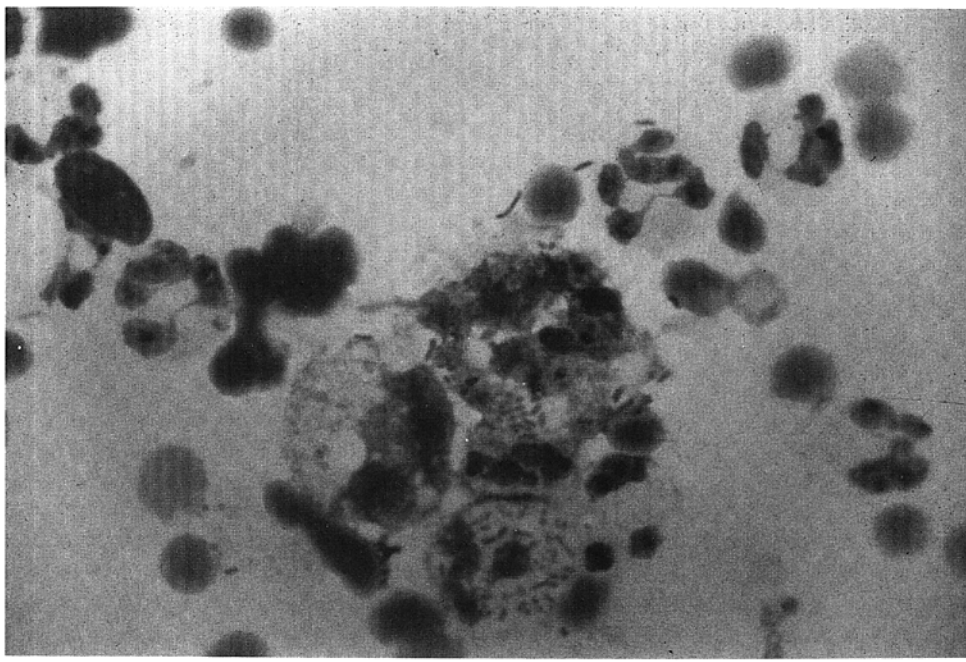

**Figure 2** Light micrographs of cells recovered by bronchoalveolar lavage from a patient with pneumonia. Many neutrophils contain multiple intracellular organisms and some extracellular organisms are present. (Diff Quick Strain, original magnification ×1000).

analysis for diagnosing nosocomial pneumonia. They reported 86% sensitivity and 96% specificity. Moreover, in patients with pneumonia, the morphology and Gram staining of the intracellular bacteria were closely correlated with the results of PSB bacterial culture.

Thus, microscopic analysis of BAL fluid may provide rapid identification of patients with pneumonia since the results are available immediately, enabling early formulation of a tailored antimicrobial therapy that can later be modified to reflect the results of the PSB culture and microorganism susceptibility. Combining the two techniques may then improve overall diagnostic accuracy and enable the development of a therapeutic strategy assuring rapid and specific treatment for most patients with pneumonia, and if both procedures are negative, allow one to withhold antimicrobial treatment with confidence (Fig. 3).

### G. Treatment

Due to the difficulty encountered in diagnosing nosocomial pneumonia in ventilated patients and in selecting antimicrobial drugs, therapy of nosocomial pneumonia is often empirical, with the initial antimicrobial regimen based on local experience and sensitivity patterns, immune competence of the patient, and severity of disease. Two factors appear to render the choice of antibiotics particularly difficult in such patients (191). First, nosocomial pneumonias are likely to result

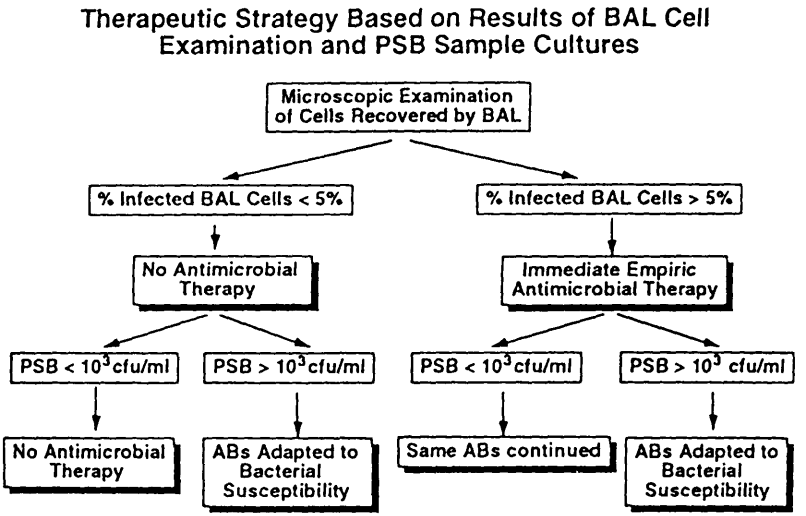


**Figure 3** Therapeutic strategy for diagnosing and treating nosocomial pneumonia in ventilated patients.

from highly resistant organisms (32,147). Second, multiple organisms are frequently cultured from patients considered to have pneumonia (147,162,165). Consequently, as stressed above, it is reasonable that evaluation of ventilated patients suspected of having nosocomial pneumonia includes the use of a reliable technique to identify patients with pneumonia and to guide the choice of antimicrobial treatment.

When no technique (or an unreliable technique) is used, empirical choices of initial antimicrobial agents must be made for suspected cases of nosocomial pneumonia. Selected therapy should be effective against *S. pneumoniae* and *H. influenzae* and broad enough to ensure coverage for aerobic gram-negative bacilli, including such highly resistant organisms as *P. aeruginosa*, *Serratia marcescens*, and *Acinetobacter* spp. Moreover, treatment cannot ignore the increasing role that other gram-positive bacteria like methicillin-resistant *S. aureus* play in numerous cases. On the basis of these considerations, several regimens have been administered for the empirical treatment of nosocomial infection. Combination therapy with an aminoglycoside and a β-lactam has long been the cornerstone of therapy (217). In special situations, coverage of other organisms has to be considered, e.g., oral anaerobes when obvious aspiration has occurred and *Legionella* pneumophila in certain hospitals.

The development of new broad-spectrum antibiotics, such as monobactams and third-generation cephalosporins and carbapems, has made monotherapy possible for the treatment of nosocomial pneumonia. Several controlled studies have compared the therapeutic outcome of monotherapy or combination therapy (218–221). Success rates were claimed to be identical or even higher in the monotherapy group when compared to results obtained with combination therapy. However, these studies included patients on clinical grounds alone, and a more rigorous comparison of these two strategies based on follow-up of accurate sampling techniques are needed before monotherapy can be strongly recommended (222). Furthermore, in patients with severe infection due to *P. aeruginosa* or other multiresistant bacteria such as extended spectrum β-lactamase *Klebsiella pneumoniae* or *Acinetobacter* spp. combination of β-lactam with an aminoglycoside is likely to produce a better outcome than monotherapy (223). Moreover, the risk of the emergence of resistant microorganisms during such therapy is considerable and has been suggested as an additional reason to use two different classes of antibiotics (224).

The duration of treatment of nosocomial pneumonia is also controversial. In some cases, such as those due to highly resistant organisms, treatment may be indicated for longer than 3 weeks, although there is no clear data concerning the definition of a successful bacteriological treatment in this setting. In some cases, it is impossible to eradicate the original pathogen from tracheal secretions despite clinical improvement. The continued presence of a tracheal prosthesis undoubtedly contributes to this persistence of potential pathogens in airways.

### H. Prevention

Conventional infection control approaches, such as adapted unit design, staff training and motivation, barrier isolation techniques, monitoring of respiratory equipment for bacterial contamination, and active infection surveillance and reporting program, effectively prevent acquisition of many pathogens and reduce infection in the ICU (225). As indicated in Table 14, some very simple, no-cost measures, such as keeping the oropharynx clean by careful suctioning of glottic secretions (185), judicious use and prompt removal of useless nasogastric tubes, placing patients in a semi-recumbent position (226), and removing tubing condensate with minimal exposure to the patient, may have tremendous impact on the frequency of nosocomial pneumonia in mechanically ventilated patients. Unfortunately, these measures are often neglected in clinical practice.

As elevated gastric pH has been correlated with overgrowth of gram-negative bacilli in the stomach and with increased risk of nosocomial pneumonia

**Table 14** Summary of Methods to Reduce the Frequency of Nosocomial Pneumonia in Mechanically Ventilated Patients

| |
|---|
| Infection control |
| Adapted architectural design of the ICU |
| Adequate number and quality of medical, nursing and ancillary staff |
| Surveillance in the ICU |
| Education and awareness programs |
| Handwashing and/or barrier precautions; remove gloves between patients |
| Check technique for suctioning patients |
| Careful suctioning of glottic secretions |
| General principles |
| Treatment of patient's underlying disease |
| Keep patient's head elevated at $\geq$30 degrees |
| Reevaluate need and drugs used for stress-bleeding prophylaxis |
| Assess nutritional status and need for tube feeding |
| Extubate and remove nasogastric tube as clinically indicated |
| Controlled use of antibiotics |
| Respiratory care equipment |
| $\geq$48-hr circuit changes (tubing and humidifier) for mechanical ventilators with humidifiers; no changes for circuits with heat-moisture exchangers |
| Careful removal and attention to tubing condensate |
| Never transfer equipment/devices to other patients |
| Care of in-line medication nebulizers |
| Proper disinfection of ventilator tubing bags and spirometer |

*Source*: Ref. 17.

(vide supra pathogenesis), the need for stress-bleeding prophylaxis and the type of drugs used for that purpose should also be carefully weighed.

Finally, a very important but less evaluated measure is the adoption of an antibiotic policy in the ICU. It would limit the emergence of resistant bacterial strains, discourage the prescription of useless antibiotics and probably reduce the cost of management of these patients.

Therapeutic prophylactic measures might include the use of endobronchial antibiotics and "selective digestive decontamination." Several authors have used endobronchial antibiotics in an attempt to reduce the incidence of nosocomial pneumonia (227,228). Results of studies using gentamicin aerosol (227) or an aminoglycoside-polymyxin B combination (229) were disappointing. After early encouraging reports, the final phase of the study showed emergence or antibiotic-resistant pathogens and increased pneumonia-related mortalities (227). Based on these data, routine use of prophylactic endobronchial antibiotics should not be recommended. Recently, several groups, particularly in Europe, have used topical prophylactic antibiotics to decontaminate the oropharynx and gastrointestinal tract in patients at high risk for nosocomial pneumonia. The rationale of this preventive method is that oropharyngeal or gastrointestinal bacterial flora appear to be a significant source of airway colonization in hospitalized patients (230). To date, more than 25 reports have been published describing the impact of selective digestive decontamination on the occurrence of nosocomial infection and the outcome of ICU patients (231). Results of these studies are, however, troublesome. Despite the clear demonstration of decreases in colonization and in gram-negative pneumonia (if we accept the criteria used by reporting authors for defining pneumoniae), very few investigations, with the exception of those involving trauma patients, have shown a reduction in mortality (232). The outcome of serious illness is very heavily weighted by the occurrence of infection, particularly gram-negative infection, and these results, by failing to demonstrate improvement in the mortality rate, are disappointing. Very recently, data indicated that the prolonged use of SDD in ICU patients brings about a sharp change in the ICU ecology with the development of resistant microorganisms (233). Therefore, careful and continuous microbiological monitoring must always be included in the survey when adopting a selective digestive decontamination strategy. Larger controlled studies using this approach are needed before the impact on morbidity, mortality, and the emergence of resistant bacteria can be fully evaluated (234).

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# 13

# Mucus Physiology and Pathophysiology

## Therapeutic Aspects

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## I. Introduction

Airway surface fluid (ASF) is a nonhomogeneous, viscoelastic, adhesive fluid containing water, carbohydrates, proteins, and lipids (1). It is a product of the respiratory system and is transported from the lower respiratory tract into the pharynx by airflow and the mucociliary transport system. ASF provides a protective milieu for the airways; its composition and physical characteristics allow for normal ciliary activity and airway hygiene. Respiratory secretions also contain immunoglobulins and protect the epithelium from drying. Expectorated sputum consists of lower respiratory tract secretions plus nasopharyngeal and oropharyngeal material including saliva, food particles, microorganisms, cells, and foreign debris. When disruption of normal secretory or mucociliary clearance processes occur, abnormal respiratory secretions can impair pulmonary function, reduce lung defenses, and increase the risk for infection and possibly neoplasia (2,3).

ASF consists of two phases: a superficial gel or mucus layer and a liquid or periciliary fluid layer that bathes the epithelial cilia. These two layers are probably separated by a thin layer of surfactant (4). In health the mucus layer is about 2–5 μm thick in the trachea and extends from the bronchioles to the upper airway. The depth of mucus does not appear to vary a great deal throughout the tracheo-

bronchial tree, but the mucus layer may become discontinuous in the smaller airways (5). The serous layer lies between the cellular surface and the mucus layer at a depth that is just less than the height of a fully extended cilium. This low viscosity layer minimizes resistance to ciliary motion and helps to maintain mucus hydration. According to model studies, mucociliary clearance is critically dependent on maintaining the depth of periciliary fluid (6).

The study of normal ASF involves obtaining samples from laryngectomized subjects, bronchial lavage from healthy nonsmokers, bronchial aspirates from healthy animals, or secreted material in vitro from animal trachea and from human bronchial explants. More frequently, the study of airway secretions consists of examining expectorated sputum, but contaminating material or small sample size can give misleading information. The normal daily volume of respiratory secretion is quoted to be between 10 and 100 ml/day (7). The total production of ASF is probably much higher than the volume arising at the larynx due to absorption of water through the lower bronchial tree via active ion transport mechanisms (8). Expectorated sputum is a sign of respiratory disease and indicates excessive production (hypersecretion) or retention (impaired clearance), as occurs in patients with respiratory infection, bronchitis, asthma, bronchiectasis, and cystic fibrosis.

## II. Biochemistry

The composition of airway mucus is about 95% water, 1–2% protein, 1% glycoprotein, and 1% lipid (9). Locally produced proteins include lysozyme, lactoferrin, IgA, IgE, and proteins attached to carbohydrates and lipids. Some albumin may be locally produced and transported by normal mechanisms (10), but the occurrence of large amounts of serum albumin in samples of respiratory tract fluid indicates the presence of bronchoalveolar inflammation or noncardiogenic pulmonary edema (11).

Mucus can be separated into two fractions by dialysis; the nondialyzable fraction consists of mucus glycoproteins (MGP), plasma-type glycoproteins, proteins, and lipids (12,13). Proteins constitute 10–25% and lipids contribute 20–30% of the nondialyzable fraction. Lipids, including neutral lipids, phospholipids, and glycolipids, may be derived from serum transudation and mucosal production, but their origin has not been well established. Lipids may be produced in situ and could play an important role in both mucociliary and cough clearance (14).

Epithelial mucins are glycoconjugates in which carbohydrate side chains are linked to a polypeptide backbone by O-glycosidic bonds between *N*-acetylgalactosamine and serine or threonine. The mucin macromolecules are 70–80% carbohydrate, 20% protein, and 1–2% sulfate bound to oligosaccharide side chains. The sugars found in mucus are typically fucose, galactose, *N*-acetylglucosamine,

*N*-acetylgalactosamine, and sialic acid (*N*-acetylneuraminic acid). Serine, threonine, and proline represent 40% of the amino acid content of the peptide backbone. Under the electron microscope, mucin units are polydispersed, flexible, threadlike structures ranging in mass from 100 to 400 kDa.

The rheological properties of mucus depend on the crosslinking of the mucin chains into a polymeric macromolecular network (15). The individual glycoprotein chains are held together by low energy, noncovalent bonds (ionic, hydrogen, and Van der Waals forces) forming a "tangled network." This polymeric, tangled network appears capable of a remarkable degree of swelling and expanding upon release from the epithelial secretory cell granules (exocytosis). The volume change of the mucin gel depends, in part, upon the degree of ionization of the gel (16).

## III. Regulation of Secretion

Airway surface liquid is produced and secreted by epithelial mucous (goblet) and serous cells and by the submucosal glands. The macromolecules that comprise the mucin fraction of respiratory tract secretions are produced mainly by three cell types located within the airway surface epithelium and the submucosal glands (7,13,17). The volume of the submucosal glands is as much as 40 times that of the goblet cells, indicating that the mucus production capacity of the goblet cells is probably only a fraction of that of the mucous and serous cells within the submucous glands. However, under basal conditions, the submucosal glands may not contribute as much as their capacity would indicate, since their main function may be to provide a rapid, large output of mucus on demand. Epithelial ciliated cells are about five times more common than goblet cells, and although they take up glycoprotein precursor molecules, they do not contribute appreciably to mucus production but may regulate the composition of the periciliary fluid (17).

Goblet cells can be stimulated to produce increased quantities of mucus (e.g., by inhalation of irritant gases), but they do not appear to be under direct neural control (17). Goblet cells are prominent in the central large airways, becoming scant in the distal airways. Irritation and inflammation of the epithelium may cause basal cells to differentiate into goblet cells; this is characteristic of chronic bronchitis and asthma.

Goblet cells incorporate mucin precursors and appear to be an important source of mucous glycoprotein. Mucous glands have a significant store of mucus that is rapidly available on demand. Submucosal glands comprise about 60% of the secretory cell mass in the trachea. Whereas the mucous cells of the glands and mucosal epithelium appear to be the main source of the mucous gel component of airway secretions, the serous cells of the glands and ciliated epithelial cells are

probably responsible for the production of the periciliary fluid. Serous cells also appear to be responsible for IgA transfer into the liquid layer.

Submucous glands respond to both direct irritant and neural reflex stimuli (17). Glands are common only in the larger central airways. The ciliated ducts of the submucosal glands arise from the mucosal epithelial surface as evaginations and lead into collecting ducts lined by tall, columnar cells that stain strongly eosinophilic. The multiple branched secretory tubules that arise from the collecting ducts are lined by mucous and serous cells. The secretory granules of the mucous cells stain intensely for acidic mucoproteins, but both types stain positive for PAS and contain complex carbohydrates. Serous cells contribute lysozyme, lactoferrin, and the secretory component for dimeric IgA.

Clara cells, found only in airways of about 1 mm in diameter, appear to be progenitor cells for mature goblet cells. In states of chronic airway irritation Clara cells may form goblet cells and produce mucin (18). These cells may also secrete surfactant lipids. Serous cells have recently been reported in normal human small airways (19), also possibly originating from Clara cells.

A rich neural innervation exists in the airway mucosa and submucosa, and cholinergic, adrenergic, and peptidergic nerve fibers surround the submucosal glands (20). Cholinergic nerve fibers occur throughout the airway, extending into the terminal bronchioles. Vagal nerve stimulation increases mucus secretion from the submucosal glands (17). Muscarinic receptors occur on submucosal glands and airway epithelium; cholinergic agonists are potent stimulants of submucosal gland secretion and ion and water transport across airway epithelium. Cholinergic stimulation augments the release of mucus from both mucous and serous cells, so that protein concentration and viscoelastic properties show little change from unstimulated glandular secretion (21,22). Anticholinergic drugs have only a small effect on sputum volume and viscosity under basal secretory conditions, and quaternary compounds like ipratropium bromide appear to have no effect whatsoever on mucus viscoelasticity (23) and no significant effect on mucociliary transport in normal subjects (24).

Sympathetic nerves also innervate the submucosal glands, but they appear to be less important then cholinergic innervation as far as mucus secretion. Stimulation of sympathetic nerves increases both mucus and fluid secretion primarily through the alpha-adrenergic system (25). Stimulation of sympathetic nerves increases submucosal gland mucus secretion. This effect is almost completely abolished by alpha-adrenoceptor blockade. Alpha- and beta-agonists stimulate submucosal gland secretion in human airways. Whereas alpha-adrenergic agonists primarily stimulate fluid secretion, beta-adrenergic agonists stimulate the production of secretions with higher protein and sulfur contents and with small amounts of lysozyme (21). A higher density of beta-receptors occurs on mucous cells and airway epithelial cells so that beta-agonists produce mucus with higher viscosity and lower elasticity. Alpha-receptors are localized to serous cells so that

alpha-agonists produce a secretion with low viscosity and, as stated above, cholinergic agonists stimulate secretions from both submucosal gland cell types.

The nonadrenergic noncholinergic or peptidergic nervous system appears to regulate airway mucus secretion via peptide neurotransmitters or neurokinins (25). Vasoactive intestinal peptide (VIP) has been localized around submucosal glands. VIP inhibits macromolecular secretion across the epithelium (21). These noncholinergic inhibitory nerves may influence mucociliary transport. Stimulation of VIP receptors activates adenylate cyclase, which increases local cyclic AMP concentration. The peptidergic nerves are distributed with cholinergic nerves, and VIP may function as a cotransmitter with acetylcholine.

Substance P is localized to afferent nerves in the airway and can promote mucus secretion and plasma extravasation into the airway (26,27). Damage to airway epithelium can expose afferent nerve endings to stimulation by inflammatory mediators. The C-fiber endings can be stimulated by mediators causing bronchoconstriction, mucus secretion, mucosal edema, and plasma extravasation into the airway lumen. The neurokinins liberated from local mucosal axonal circuits appear to cause both direct and reflex stimulation of glands.

## IV. Viscoelastic Properties of Mucus

Due to the crosslinking of glycoproteins, mucus rheological behavior is described as viscoelastic, having characteristics of both a liquid and a solid (1,28–30). Viscosity is the absorption of energy from an object moving through a substance and thus the resistance to flow. Elasticity is the recoil energy transmitted back to this object. With ideal fluids, viscosity is independent of the applied stress. With viscoelastic liquids such as mucus, viscosity decreases with increasing stress or rate of strain (shear rate). Mucus responds to stress with an initial solidlike deformation followed by a viscoelastic deformation and finally by a period of steady flow in which the rate of deformation is constant. Only partial recovery of the strain follows removal of the stress indicating a permanent deformation of its gel structure.

Mucus exhibits shear thinning, i.e., following exposure to high shear forces, it shows a decreased viscosity at low shear rates. Some shear thinning may be permanent with a permanently reduced viscosity (altered molecular structure), while some shear thinning may be reversible (thixotropy). When sputum is obtained by aspiration under pressure, it undergoes shear thinning, dilution by irrigation fluids, and incorporation of air bubbles.

Water can bind to mucus glycoprotein (MGP) macromolecules and influence viscosity. Viscosity can be increased by dehydration of the mucus (as can mucus-epithelium adhesion). Mucus viscoelasticity increases with acidic pH (31), causing reduced mucociliary clearance. In purulent sputum the correlation be-

tween viscosity and dry weight of solids is poor, which may explain why mucous glycoprotein content is a poor index of viscoelasticity in chronic bronchitis, bronchiectasis, and cystic fibrosis.

Changes in mucus viscosity and elasticity are interrelated (32). Optimum mucociliary clearance of airway mucus is located at the low end of the normal range of viscoelasticity (33–35). A decrease in clearance rate (transport) occurs with increasing mucus elasticity and with increasing viscosity. Increasing viscosity with constant elasticity causes a pronounced decrease in the mucociliary transport rate (36). Decreasing mucus viscosity alone results in an increased transport rate and may explain the improvement in sputum mobilization following hydration or mucolytic drug therapy.

Another measure of elasticity is spinnability (*Spinnbarkeit, filance*)—the thread-forming ability of mucus under the influence of large amplitude elastic deformation. Spinnability has been correlated positively with mucociliary clearance (37) and negatively with cough clearance (29). Adhesivity is the ability of mucus to bond to a solid surface measured as the force of separation between one or more solid surfaces and the adhesive material. This is dependent on mucus surface tension, hydration, wettability, and contact (dwell) time. Adhesivity has been found to correlate inversely with both mucociliary clearance and cough clearance (29,38).

## V. Mucociliary Clearance

Mucociliary clearance can be measured by visualizing the movement of particles such as teflon disks, tantalum powder, or charcoal powder placed on airway during bronchoscopy. An inert, radiolabeled tracer can also be placed on the airway and its clearance monitored with scintillation counters or a gamma camera. Whole lung clearance is measured by having the subject inhale an aerosol of radiolabeled tracer and then scanning over defined regions in the proximal and distal lung.

A decrease in mucus transport velocity occurs with increasing airway generation (39); otherwise stated, the rate of mucus transport accelerates from the peripheral airways to the larynx. Impaired mucociliary transport leads to retained secretions in the airways and increased susceptibility to infection. Accumulation of mucus could increase the risk of destructive, inflammatory and neoplastic lung disease by prolonging the contact time between inhaled materials and the airway mucosa (40). Since cough clearance is ineffective in peripheral airways (41), mucociliary clearance is relatively more important in cleansing and protecting these lung regions.

The structure and function of the epithelial cilia have been the subject of excellent reviews (6,42,43). The periciliary fluid appears to originate from multiple sources, the most important of which are active water and ion transport across

the airway surface epithelium (8,17). If the depth of the periciliary fluid is too shallow, the cilia are unable to beat effectively and may become entangled in the mucus gel layer. On the other hand, a fluid layer too deep may not allow the cilia to make contact with the mucus gel layer, thus decreasing mucociliary clearance. The depth of the periciliary layer may be regulated by homeostatic mechanisms.

The viscoelasticity of the mucus layer contributes to the effectiveness of the mucociliary interaction, but the surface interaction between mucus and cilia also play a critical role. Ion and water transport across the surface epithelium appear to be crucial to this interaction. By generating local osmotic gradients, epithelial ion transport processes regulate the depth and composition of the periciliary sol layer (8,44). Ion transport is regulated by neurohumoral mechanisms, cholinergic and adrenergic agonists, prostaglandins, substance P, VIP, and bradykinin (45).

The transport velocity of mucus simulant gels is directly related to mucus elasticity and the depth of the periciliary fluid, and it is inversely related to mucus viscosity (28). An ideal viscoelastic ratio may exist for optimal mucociliary interaction, an increase in viscosity, and/or a decrease in elasticity would result in a reduced transport rate. Transport by cough or airflow interaction depends inversely on viscosity, elasticity (spinnability), and adhesivity (29). Mucus that is elastic rather than viscous is transported well by ciliary action, but less well by coughing (1).

## VI. Airway Secretions in COPD

### A. Irritant Exposure, Smoking, and Lung Cancer

Acute exposure to irritants causes hypersecretion of a watery, easily cleared mucus that might be derived from preformed goblet cell secretions (29). Similarly, asymptomatic smokers produce a watery mucus that is transported 30% faster than normal mucus on the frog palate (45a,46). However, in vivo mucociliary clearance is not increased in the light smoker, probably because of ciliary damage.

Most chronic smokers produce a rigid but elastic mucus with more sialic acid and fewer fucose residues (47). This reduces ciliary clearability back to normal levels while depressing cough clearability (3). It has been postulated that impaired mucus clearance in chronic smokers can lead to prolonged contact of irritants with the airway epithelium and so promote cellular metaplasia and cancer. However, some lifelong smokers seem to escape COPD and cancer. Preliminary evidence suggests that these smokers have mucus that retains viscoelasticity favorable for cough clearance. On the other hand, mucus from a small number of patients with primary adenocarcinoma who never actively smoked had viscoelasticity unfavorable for both cough and ciliary clearance (48).

The diagnosis of chronic bronchitis is made by a history of sputum production for a continuous period of at least 3 years and reflects mucus gland hypertro-

phy and goblet cell hyperplasia (49). Patients with asthma who are hypersecretors share many of the pathological features felt to be characteristic of chronic bronchitis (50,51). The findings of inflammation are common to both conditions, even though certain features of inflammation may be unique to each disease. Whereas infiltration by eosinophils, basophils, and mast cells is commonly seen in the airways of asthmatic patients, neutrophils are usually seen in the sputum of bronchitic patients. Bronchial hyperresponsiveness to multiple stimuli is not uncommon in bronchitis, but it is the *sine qua non* of asthma.

The presence of inflammation within the airways appears to be related to the development of nonspecific hyperresponsiveness as well as to the development of increased sputum production in both asthma and chronic bronchitis. Both asthma and chronic bronchitis have increased numbers and more widespread distribution of goblet cells into the peripheral airways (50). Goblet cell hypertrophy and hyperplasia occur in chronic smokers. Increased mucous gland volume is seen in asthma, chronic bronchitis, bronchiectasis, and cystic fibrosis (49,51a,52). In chronic bronchitis the ratio of the height of the mucous glands between the luminal edge of a cartilage ring and the surface epithelium (Reid index) is increased. In chronic airways disease the proportion of mucous to serous cells increases in the submucosal glands and the mucus produced contains greater amounts of acidic mucopolysaccharides that are resistant to the enzyme neuraminidase (53–56).

When the mucociliary system becomes overwhelmed, cough and sputum expectoration becomes vital for airway hygiene. Depressed mucociliary transport is thought to contribute to the pathology of both asthma and chronic bronchitis (57–61). Inhaled pollutants, anesthetic gases, oxygen, and pharmacological agents in addition to congenital abnormalities in ciliary and mucus secretory function can cause depressed mucociliary transport rates (60). Purulent sputum contains leukocytes, bacteria, and cell products that may impair ciliary function (62–64). Neutrophil elastase, eosinophil major basic protein, and bacterial products damage the airway epithelium (65,66). Inflammation, infection, and trauma to the epithelium and submucosa depress mucociliary clearance and stimulate afferent neural receptors (67,68). Both anatomical disruption and ciliary impairment contribute to the mucociliary transport depression in patients with chronic bronchitis (60).

Ciliary inhibitory factors liberated by disease processes include inflammatory mediators and released enzymes, bacterial products, and sputum factors (69, 70). Reduced mucociliary transport in asthma may be exacerbated by chemical mediators (histamine, PAF, leukotrienes) that can change ciliary activity and microvascular permeability (65,71). Plasma extravasation and mucosal edema in asthma and chronic bronchitis add to small airways obstruction (51). In addition to delivering chemical mediators into the airway mucosa and lumen, extravasated plasma can cause epithelial cell sloughing, adding to the debris within the mucus

layer. Plasma exudation and fibrin formation can potentially change the viscoelasticity of the mucus, impair the surfactant properties of the airway lining material, promote inflammatory cell entry into the lumen, and cause small airway obstruction.

### B. Clinical Relevance of Abnormal Airway Secretions

A number of factors impair mucociliary function in COPD. Epithelial damage, inflammation, alterations in gas exchange, and neurohumoral factors all can cause impaired mucociliary transport and alterations in respiratory tract secretions. Hypersecretion of mucus, changes in mucus viscoelasticity and surface adhesion, and impaired ciliary function leads to entrapped mucus. Retained airway secretions can form tenacious mucous plugs and bronchial casts that cannot be expelled by coughing (57). Airway plugging causes impaired ventilation resulting in lower ventilation-to-perfusion ratios. Increased airways resistance to airflow and air trapping result in hyperinflation of the chest and inspiratory loading of the respiratory muscles leading to fatigue.

Respiratory muscle fatigue combined with airway plugging can render cough less effective. Airway plugging provides a milieu for microbial colonization leading to infectious bronchitis, bronchiolitis, or pneumonia. Airways obstruction can also lead to air trapping, uneven ventilation, and increased work of breathing. Ventilation-perfusion mismatching leads to impaired gas exchange and respiratory failure. When airways are totally occluded by secretions, the spirometric pattern may be one of restriction rather than obstruction. The forced vital capacity (FVC) is reduced along with the forced expiratory volume in one second ($FEV_1$) so that the $FEV_1$/FVC ratio is relatively preserved.

Retained airway secretions can trap microorganisms leading to infection and further lung damage. Airway obstruction tends to reduce aerosol deposition in the smaller, peripheral airways (58,72). This may protect the peripheral airways from inhaled particles; but it also makes aerosol therapy more complicated.

## VII. Therapy of Mucus Clearance Disorders

### A. Environmental Modification

Inhaled irritants (smoke, fumes, and vapors) can directly stimulate airway mucus secretion. Pathological stimulation of mucus secretion may cause excessive secretions with low viscosity, i.e. bronchorrhea. Avoidance of cigarette smoke and occupational irritants are important treatment goals.

### B. Medications

Mucolytic agents are meant to alter the composition and crosslinking of mucus, with the intention of improving its clearability by ciliary action and/or cough.

Direct-acting mucolytic agents include those that (a) break disulfide bonds (intra- and intermolecular), (b) degrade the mucin peptide core (proteolytic enzymes) or oligosaccharide side chains, and (c) reduce the interactions between neighboring mucin macromolecules resulting from ionic and hydrogen bonds (1,73,74). A variety of other treatment approaches are aimed at improving the rheological characteristics of the mucus. These include treatments that degrade the macromolecules that cause additional crosslinking of mucus in disease (e.g., DNA, F-actin), mechanical degradation of mucus by high-frequency oscillation, and treatments designed to change the water content of the mucus by altering transepithelial ion fluxes.

*N*-acetylcysteine (NAC) and related compounds break disulfide crosslinks stabilizing the mucin network, thus decreasing mucus viscosity (75). NAC can be instilled directly into airways under bronchoscopic visualization to relieve airway plugging (76). Dissociating agents such as 4 M urea are effective mucolytics in vitro (110), but they may be too harsh for clinical use. Hypertonic saline has potential as a mucotropic agent by shielding the excess of fixed negative charges that develop on mucins in airway disease (77). The efficacy of proteolytic enzymes in diseases associated with airway plugging remains unproved. The value of direct-acting mucolytics is limited by the fact that they can potentially overliquefy mucus, making it too thin for effective clearance (28,78).

Cough suppressants have a limited role in the therapy of mucus clearance defects, and the combination of a cough suppressant with an expectorant is completely illogical. Although expectorants can theoretically increase glandular secretions and so assist cough clearance, this has not been well studied. Expectorants do not alter ciliary beat frequency or mucociliary clearance favorably or unfavorably. Although the mechanism of action of the expectorants is unclear, their use is supported by the demonstration of clinical efficacy. It may be that by altering epithelial ion permeability, the expectorants loosen sputum that is adherent to the epithelial surface and thus increase the effectiveness of coughing.

Few mucolytic agents have been demonstrated to be effective in assisting airway clearance. An ideal mucolytic medication should be well tolerated systemically and should thin abnormally viscous mucus and thicken mucus that is too watery for proper clearance. If possible, the physical and transport properties of mucus and ciliary function should be assessed before and during mucolytic therapy. As this is usually not possible, careful clinical assessment and follow-up is vital to ensure that improved rather than impaired mucus clearability results from the therapy.

Mucoactive agents are meant to increase mucus clearance from the airways by their effects on the rheology of mucus and ciliary activity or lung mechanics (73,78,79). Adequate hydration of airway secretions is best accomplished by adequately hydrating the patient, but inhaled aqueous mist may retard insensible water loss from the airway. Overhydration can lead to plasma exudation into the

airways and mucosal edema. Inhaled liquids must be carefully controlled for tonicity, pH, and temperature. Improving the patient's hydration may increase fluid transport into airway mucus, but the clinical results of moderate hydration in patients with chronic bronchitis show little effect on sputum volume or ease of expectoration (80).

Oral expectorants are thought to increase airway mucus secretion by acting on the gastric mucosa to stimulate the vagus nerve. Oral emetics stimulate the cholinergic pathway to the airway submucosal glands, causing them to secrete increased quantities of mucus. Other mucokinetic agents include bromhexine, guaifenesin, ipecac, and various salt solutions (73). Bromhexine appears to act directly on mucous glands and may stimulate cholinergic activity with reflex glandular secretion. Guaifenesin (glycerol guiacolate) appears to be a gastric stimulant and may stimulate mucus secretion reflexly. It has little, if any, mucolytic action in vitro, but acts as a demulcent to enhance mucociliary clearance at doses close to the emetic range. Inorganic salt solutions (ammonium, potassium, and sodium) are hypertonic electrolyte solutions that stimulate the gastrointestinal mucosa resulting in reflex stimulation of the submucosal glands. The effectiveness of these agents in the treatment of asthma and chronic bronchitis is anecdotal. Rather than acting through the "gastropulmonary mucokinetic vagal reflex," some agents such as iodides appear to directly stimulate airway mucus secretion (73,79).

Iodide-containing drugs may be given by mouth and appear to be clinically effective in enhancing sputum and mucociliary clearance, especially in patients with mucus hypersecretion (59,81). Iodides probably stimulate mucus secretion directly. Iodide appears within secretions following oral administration. Iodides also stimulate a vagal reflex that causes a mucokinetic effect inhibited by atropine. In vitro, iodides have a direct mucolytic effect on mucus macromolecules similar to the effects of acetylcysteine and other inorganic salts (73). Iodides appear to potentiate sputum proteases, and they may stimulate ciliary beating frequency.

Ambroxol is thought to stimulate surfactant secretion and is widely used in Europe for the management of chronic bronchitis (82). However, a double-blind, randomized, placebo-controlled trial in 90 patients with chronic bronchitis who had difficulty clearing secretions showed a clinically trivial benefit (82a). Exogenous surfactants have been shown to increase mucociliary clearance in animals (27) and to "improve" the clearability of mucus in newborns with RDS (46). Their use as possible mucokinetic agents should be investigated further.

Beta agonists increase ciliary beat frequency and clearance of mucus in the normal airway (2). Their role is limited in assisting sputum clearance, especially when there has been considerable ciliary damage, although beta agonist bronchodilators could improve airway clearance by reducing gas trapping and increasing airflow-dependent clearance mechanisms. The effect on the mucus secretory response appears to be secondary to cAMP production. Beta agonists alter ion and

water transport across the surface epithelium, thereby presumably contributing to the improvement in clearance. The stimulation of mucociliary transport by beta agonists occurs following administration of inhaled, parenteral, or oral formulations. Poor delivery of inhaled beta agonists into plugged or narrowed airways may impair efficacy. Although xanthines also increase ciliary frequency, these medications have not been consistently demonstrated to improve mucus clearance (83,84).

Anticholinergic compounds may decrease ciliary beat frequency and reduce mucus production. They have been used to reduce bronchorrhea (85,86). Inhaled ipratropium bromide causes few systemic effects and does not depress mucociliary transport in humans (24). In chronic bronchitis, ipratropium bromide may decrease sputum volume without adversely affecting sputum viscosity or dry weight (23).

Corticosteroids have been used to treat patients with mucus hypersecretion. They work potentially by reducing plasma exudation in inflamed airways and phospholipase A activity, thus decreasing respiratory mucus production (87,88). Inhaled cromoglycate led to a reduction in mucociliary clearance following allergen inhalation in sensitized sheep (89).

Amiloride as a sodium channel regulator, decreases water and sodium resorption from the airways. Its potential use in CF lung disease has been well documented (90,91); however, its principle of action—decreasing excessive absorption of water across the airway epithelium—could even prove useful in COPD. Other diuretics like furosemide alter epithelial membrane ion fluxes but appear to have minimal effects on mucus secretion (79).

### C. Physiotherapy and Postural Drainage

Chest physical therapy (CPT) includes the application of directed cough, forced expiratory techniques, postural drainage, chest percussion, clapping, vibration, high-frequency oscillation, and breathing exercises. Chest physical therapy may not significantly alter the outcome of acute exacerbations of COPD, even in those with severe respiratory failure. Some studies show no clear long-term clinical benefit of chest physical therapy in patients with COPD. The value of CPT in preventing postoperative respiratory complications is largely unproven, although CPT appears to be as effective as fiberoptic bronchoscopy in the treatment of postoperative atelectasis.

Chest physical therapy is most efficacious when it is accompanied by cough. Physiotherapy does not appear to improve mucociliary clearance but may assist cough clearance by promoting the formation of easily expectorated mucus globules in the large airways, freeing adherent mucus from the epithelial surface, and triggering cough receptors.

Peripheral airway secretions are mostly cleared by mucociliary transport, but this mechanism is less effective in patients with chronic bronchitis and acute severe asthma (2). Diminished mucus clearance and mucus hypersecretion leads to accumulation of lower airway secretions and airway plugging. Chest physical therapy can be used in such patients in combination with medications in order to promote sputum mobilization and expectoration, reduce airways obstruction, improve mucociliary function, and improve ventilation and gas exchange (92–94).

Hydration of inhaled air may enhance mucociliary clearance (95,96), but objective changes in lung function are not generally observed (80). Inhalation of hypertonic saline may increase mucociliary clearance, possibly by stimulating an increase in secretion output and ciliary beat frequency, and also by improving the rheological characteristics of the mucus. However, hypertonic saline can cause bronchospasm. Intermittent positive pressure breathing provides no added benefit to mucociliary clearance and no advantage toward optimal delivery of bronchodilators to the airways. The relationship between bronchodilatation, improved airflow, and sputum mobilization is complex. Improved sputum clearance leads to improved airflow, just as efficient cough requires adequate airflow. A small but significant increase in $FEV_1$ may follow chest physical therapy in patients with excess sputum production, but some studies fail to show a correlation between improved lung function and the volume of sputum expectorated, especially in those with stable COPD. Most studies have failed to demonstrate beneficial short-term effects of chest physical therapy on pulmonary function (97–99). In most studies no correlation has been found between pulmonary function tests, clinical response, and mucus clearance.

Chronic mucus hypersecretion does not by itself appear to cause airflow obstruction to progress more rapidly (49). In some patients with asthma and chronic bronchitis, a worsening of lung function, wheezing, and bronchoconstriction may follow the use of chest physical therapy, especially in those with hyperresponsive airways, scanty sputum production, and small airways disease (100). Chest physical therapy is only able to increase sputum mobilization if excessive secretions are present in the airways. Patients with cystic fibrosis, bronchiectasis, and COPD associated with mucus hypersecretion are more likely to benefit from chest therapy. Short-term benefits of CPT have been largely unrelated to long-term outcome except in studies of patients with cystic fibrosis. When evaluating the effects of chest physical therapy, the volume, composition, and transport of mucus must be considered as separate variables. In most studies sputum volume and pulmonary function have been used to assess the benefit afforded by CPT, but measurement of mucus transport rates may be more sensitive (94,101,102), and it is important to evaluate of the physical properties of expectorated secretions—not only do these change in individual patients over time, but they can affect mucus transport, making the assessment of efficacy more difficult

to interpret. For example, chest physical therapy may not improve lung mechanics, regional ventilation, or blood oxygenation in patients with bronchiectasis and chronic bronchitis even though sputum volume increases. In patients with chronic bronchitis who produce greater than 30 ml of sputum per day, chest physical therapy may improve airway conductance without increasing sputum volume (102).

Chest physical therapy combined with vigorous, directed cough is effective in clearing the airways of patients with retained secretions (94). Cough efficiency depends on high expiratory airflow rates (mucus shearing forces), which in turn depends on generation of large positive intrapleural pressures best achieved at high lung volumes. For these reasons breathing exercises are often combined with chest physical therapy. Cough is best at clearing secretions from central airways, but it may increase mucus transport from peripheral airways. Cough may normalize rates of mucus removal in patients who lack mucociliary transport (2,103).

Evidence from studies using inhaled radioaerosol techniques show that cough alone and cough combined with chest physical therapy are equivalent in promoting central airway mucus clearance, whereas combined techniques were better for accelerating clearance from the small airways (104). Forced expiratory technique (FET) appears to be more effective than cough alone and supervised directed coughing may be as effective as conventional postural drainage, vibration, and/or percussion and coughing in patients with cystic fibrosis (105–107). The forced expiratory technique may cause less bronchial compression and collapse and be more effective in clearing airway secretions in selected patients.

Postural drainage can enhance clearance of airway secretions, and it appears to act by allowing gravity to propel secretions toward the central airways and pharynx. Postural drainage acts to complement cough and mucociliary clearance. Postural drainage increases clearance of central airway secretions and sputum volume in patients with chronic bronchitis, bronchiectasis, and cystic fibrosis, and patients with cystic fibrosis may show improved pulmonary function following chest physical therapy (94). In these patients vigorous cough alone is as effective in clearing airway secretions as full chest physical therapy maneuvers and cough is more effective than postural drainage with or without combined chest vibration. When postural drainage is combined with cough, mucociliary clearance and sputum expectoration are increased. Postural drainage promotes enhanced sputum production and clearance of secretions, especially in patients with cystic fibrosis.

There are few data that percussion and vibration add to the sputum clearance produced by postural drainage alone in patients with atelectasis. Addition of percussion to conventional physiotherapy did not improve sputum yield or mucociliary clearance in most studies except possibly for patients with cystic fibrosis. Chest wall vibration alone appears to provide no measurable benefit in sputum production or mucociliary clearance, but high-frequency chest wall compression shows promise as an effective means of enhancing mucus clearance (108,109).

## VIII. Summary

Airway secretions are increased in patients with lung diseases associated with inflammation including chronic bronchitis and asthma. Normal lungs are devoid of appreciable inflammation and consequently little if any sputum is expectorated. Inflammatory cells are absent in normal mucus, but are generally abundant in the sputum from patients with chronic mucus retention. Chronic bronchitis patients have large numbers of neutrophils, whereas asthmatic patients have elevated numbers of sputum eosinophils. These cells are capable of releasing a variety of mediators that can alter the secretion and clearance of mucus. Cell debris adds DNA, lipids, and proteins to the normal respiratory secretions causing further alterations in rheology and depression of mucociliary clearance. The end results is airway plugging, which causes bronchial obstruction resulting in atelectasis, impaired lung mechanics and gas exchange, and infection.

Treatment of COPD should include measures that reduce inflammation and clear the airways. Clearing the airways will decease airways obstruction, improve gas exchange, reduce the work of breathing, and facilitate resolution of infection. Airway clearing is accomplished by directed coughing, chest physical therapy, and the use of pharmacotherapy. Reduction of inflammation can be achieved by the use of corticosteroids, while infection is treated with appropriate antibiotics. Reduction of airway hypersecretion can be achieved by using medications that reduce mediator production or antagonize their action and anticholinergics that counter excessive reflex vagal activity. Various mucokinetic and mucolytic agents such as iodides may be used to improve the viscoelasticity of mucus and enhance mucociliary clearance, cough, and physiotherapy.

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# 14

# Thromboembolic Disease as a Precipitating Factor

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## I. Diagnosis

Accurate diagnosis of pulmonary thromboembolism is difficult in normal subjects, and the difficulties are considerably greater in COPD. Diagnosis is discussed in the first section of this chapter because the problems of diagnosis are essential background to discussions of epidemiology and treatment.

### A. Clinical Findings

There is information in several studies about the diagnostic value of purely clinical data (history, physical examination, and routine tests such as chest x-rays and blood gases). As detailed in this section, the data show that these methods by themselves cannot be relied on to make an accurate diagnosis. In all published studies, clinical data have been used to select patients who are sent on for more precise diagnostic tests. The validity of excluding the diagnosis when there is a lack of clinical features has not been tested.

As part of the NHLBI-sponsored PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study, Lesser et al. (1) described 108 patients

with suspected embolism who also had COPD. Judging by the clinical data provided, most of these patients had mild or moderate COPD, and none were mentioned as being in acute respiratory failure. Pulmonary embolism was shown by angiography in 20 patients and by autopsy in one patient. The diagnosis was excluded by angiography in 73 patients and by clinical outcome analysis in the remaining 14 patients. The frequency of risk factors (e.g., immobilization, surgery) was similar in those with and without thromboembolism. The frequency of various symptoms (dyspnea, cough, pleuritic pain, leg swelling, wheezing, leg pain, hemoptysis, palpitations, and angina) was also the same in those with and without thromboembolism, as was the frequency of signs (crackles, tachypnea, tachycardia, wheezes, pleural friction rub, loud pulmonary second sound, and others). The alveolar-arterial gradient for oxygen, the arterial $P_{CO_2}$, and the chest x-ray findings were also unhelpful in separating the two groups.

This study thus showed, for patients with mild to moderate COPD, that if the clinicians had some good reason to suspect embolism, the likelihood of demonstrable embolism was about one in four. The results did not encourage the hope that analysis of the details of clinical presentation would improve the diagnostic accuracy of clinical assessment. The study gives no information about the likelihood of embolism being present in COPD patients in whom the diagnosis is not suspected clinically. It is not easy to characterize with any accuracy the gestalt that led clinicians participating in the trial to classify cases as suspected of embolism. There remains considerable uncertainty, therefore, about the a priori probability of any patient with COPD with an acute syndrome having thromboembolism.

In our experience with COPD in acute respiratory failure, the sudden occurrence of hypoxemia associated with a decrease in $P_{CO_2}$ and a deterioration in cardiovascular status justifies a search for thromboembolism. Traegers (2) has emphasized the telltale character of a sudden rise in pulmonary artery pressure with a drop in diastolic pressure, sometimes to the point of making pulmonary artery pressure identical to ventricular pressure, with disappearance of wedge pressure and inability to measure cardiac output. This is a rare event. A rise in $P_{aCO_2}$ has also been described as an indicator of embolism (3), but seems uncommon or uncommonly noticed or pursued. Acute reduction in $P_{CO_2}$ with worsening of hypoxemia has also been described with embolism in COPD and may be a more common manifestation (4). Chopin et al. (5) looked at an indicator of alveolar dead-space (the difference between arterial $P_{CO_2}$ and the maximal value of expired $P_{CO_2}$ sampled near the end of a 15-sec passive expiration) in COPD patients in acute respiratory failure, paralyzed, and mechanically ventilated. They found that this difference clearly separated 17 patients with angiographically proved emboli from 17 patients with normal angiograms, and they recommended the use of this test. In their population the test was 100% sensitive, 65% specific, and had a positive predictive value of 74% and a negative predictive value of 100%. The patients participating in this study were suspected clinically of embolism based on

a sudden onset of symptoms, unexpectedly severe hypoxia, hemodynamic evidence of acute cor pulmonale or severe hypotension, or presence of deep venous thrombosis (DVT).

### B. Radioisotope Lung Scanning

Ventilation-perfusion radioisotope scans have now been shown to be much less helpful than previously supposed, even in patients with previously normal lungs. A normal lung scan pretty well excludes embolism. A so-called high probability scan, defined as unmatched perfusion defects that correspond to segments or lobes, means that there is a greater than 85% chance of embolus. These probabilities, reasonably well established in large studies of patients free of pulmonary disease, are consistent with parallel numbers obtained for COPD patients, although the latter are based on a smaller series of patients (1,6). Both definite findings are relatively uncommon in practice, however. A reasonably certain diagnosis, yes or no, was found in only 2 of 35 cases of moderate to severe COPD by Lesser et al. (1). The so-called "moderate probability" and "low probability" scans found in 33 of the 35 patients do not provide enough definite information to make a decision whether or not to anticoagulate. In COPD of any severity, normal lung scans are not likely to occur because of the gross disturbance of regional ventilation and perfusion caused by the underlying disease. This kind of scanning is therefore very unlikely to be of use in COPD patients in general (7), and even less likely to be so in COPD patients in acute respiratory failure. Given the low utility of the test, it is possible to be concerned about complications of the procedure itself in these patients, as there has been one case report of respiratory failure precipitated by lung perfusion scanning in a patient with advanced emphysema (8).

### C. Angiography

The "gold standard" technique for demonstration of thromboemboli remains pulmonary angiography. This test may miss multiple small emboli. In addition it may be difficult to separate emboli from thrombi formed in situ. Pulmonary angiography is sometimes considered risky in COPD patients, but this concern may be exaggerated. Patients with pulmonary artery pressure greater than 70 mmHg systolic or right ventricular end-diastolic pressure above 20 mmHg had a mortality of only 3%. The risk is much less in patients with less severe disease.

### D. Computerized Tomography

The new technique of spiral volumetric computed tomography (9) may eventually replace angiography as a gold standard and, being noninvasive, may permit more extensive surveys of the incidence and importance of embolism in COPD.

### E. General Consideration

Venous thromboembolism on a small scale is probably a common event. As long as only small emboli occur at infrequent intervals and as long as the normal mechanisms for dissolution of clots and recanalization of pulmonary arteries are working well, this process will be able to continue in persons with normal lungs without causing appreciable symptoms or signs. The disease of thromboembolism occurs when patients suffer large emboli or when multiple small emboli accumulate more quickly than they are dissolved. All the tests for identifying emboli are more effective when the emboli are large. The association of negative tests with low clinical risks does not necessarily imply that a negative test means a complete absence of emboli. Instead, it may imply that emboli on a scale too small to be detected by the test are likely to be manifestations of a low-grade process that can be well tolerated by the patient. If this is the case, the quantitative conclusions about accuracy of diagnostic tests taken from patients with normal lungs may easily not apply to COPD patients, because the latter are much more vulnerable to small emboli. An embolus too small to be detected by angiography or lung scanning and therefore too small to give a positive test even in normal lungs with current methods could have gas-exchange and hemodynamic effects of considerable importance in a COPD patient.

## II. Epidemiology

The incidence of pulmonary thromboembolism in COPD patients is uncertain and is likely to remain so because of the difficulty of making a certain diagnosis.

The first complete anatomical study was performed by Bignon et al. (10), who used postmortem angiography to locate thrombi in 52 cases of COPD patients who had died in acute respiratory failure in an intensive care unit. They found clots with the appearance of thromboemboli in the pulmonary vascular tree of 45 (87%) of the cases. Five cases (11%) had more than 50% of the vascular tree obliterated. Of these, 4 cases had single massive emboli obstructing the main pulmonary artery or most of its branches, with older, more peripheral emboli. The fifth had multiple emboli of different ages. Eleven additional cases (24%) had obstructed vessels equivalent to the blood supply of at least one lobe, and 18 (40%) had obstructed the equivalent to the blood supply of less than a lobe but more than a segment. In all cases emboli were widespread, involving small peripheral arteries more often than main ones. They were usually of different ages, both recent fibrinous ones and older organized and adherent ones. In 8 cases there were chronic, organized, fibrous, partially recanalized clots or fibrinous thickening of the intima. In addition to complete obliteration of the lumen, there were many partial occlusions, with clots moving freely in the radiopaque medium, giving more-or-less fragmented filling defects on angiogram. Pulmonary infarcts were

only seen in 39 (75%) of the 45 cases with emboli. In most of these cases infarcts were multiple, on average three per patient. Thromboembolism was considered the main cause of death in the 30% of the patients who had obstructed the equivalent of the blood supply to one lobe or more and was estimated to have contributed to the cause of death in another 20%. Many of these patients had right ventricular hypertrophy. Seven had intracardiac thrombi. Only 11 (25%) of the cases had venous thrombosis at autopsy. The thrombi in the lung may have migrated before autopsy, or the origin of emboli could have been the right ventricle, but many thrombi may have formed in situ.

This study was a witness to an era when mortality during episodes of acute respiratory failure in COPD was higher than it is today. Since that time it has been customary in many places to treat such patients with low-dose heparin, a practice that has been associated in the Paris experience with a diminution of approximately 50% in mortality and possibly with lower rates of autopsy findings of thrombi and emboli.

Several more recent studies have given estimates of the frequency of thromboembolism in living patients. None of these has looked exclusively at COPD patients in acute respiratory failure, and the criteria for diagnosis and for selection of patients to investigate for thromboembolism vary from study to study. Lesser et al. (1) performed angiography on 108 COPD patients suspected clinically of having thromboembolism, most of whom were not in respiratory failure. They made a positive diagnosis in 21 of them (19%). Because they did angiography on only those patients who they thought might have emboli on the basis of (1) evaluation of a senior physician, (2) a decrease in $CO_2$ with a sudden drop in oxygen, or (3) a sudden drop in blood pressure, these data probably underestimate the true incidence among patients with acute symptoms. Harris et al. (11) did a retrospective study of all patients admitted to a respiratory intensive care unit in a year when heparin prophylaxis was not in use. Forty percent of these 98 patients had COPD as their main diagnosis. In 13 of the 98 a diagnosis of thromboembolism was made. It is noteworthy that only 15 patients were investigated in order to find these 13 cases. This suggests either that the clinicians in this study were much better than others at making an accurate clinical diagnosis (positive or negative) of thromboembolism or that their threshold for investigation was rather high. If the latter is true, their estimate of incidence of 13% may be low.

Chopin et al. (5) found clinical indications to suspect emboli in 66 of 281 COPD admissions (23%). Of those in whom they could perform angiograms, half had emboli demonstrated. As in other clinical studies, this incidence (33/281, or 12%) is an underestimate because emboli are likely to have been present in some patients in whom it was not suspected and not investigated.

It is assumed that almost all pulmonary thromboemboli originate in veins of the leg. Another approach to assessing incidence is therefore to look for evidence of deep venous thrombosis (DVT) in populations of patients. Moser et al. (12)

performed radioactive iodine fibrinogen scans on the legs of 34 consecutive patients in acute respiratory failure (of all types) in whom it was feasible and found only 3 abnormal ones. It was not stated how many of these patients had COPD. Prescott et al. (13) did either venograms or radioactive fibrinogen scans in 45 COPD patients and found that only 2 had DVT in the first week of admission and 2 developed DVT after the first week. These scant data suggest a rate of DVT of 8–9%.

The discrepancies between results of various studies may be explained by differences in study populations, differences in techniques for identifying thrombi and emboli, and possibly by differences in approach to prophylactic anticoagulation. The difference between the autopsy incidence of emboli and the rate of clinical diagnosis of emboli in life in COPD patients with acute respiratory failure certainly raises the concern that clinical assessments are insensitive to occurrence of embolism and/or in situ thrombi. In the final analysis it seems clear that some cases of acute respiratory failure are caused by pulmonary embolism, but it is impossible to know how many. It is likely that emboli are present in more than 15% of cases. The importance of in situ thrombosis in progression of the disease is uncertain, and, as in normal people, the speed of resolution of emboli and the frequency of nonresolution or incomplete resolution is unknown.

## III. Therapeutic Approach

### A. Prophylaxis

The difficulty of diagnosis of thromboembolism in these patients prohibits the use of a single rigid approach. Many experts consider it reasonable to provide prophylactic anticoagulation with low-dose or adjusted-dose heparin in patients with COPD in acute respiratory failure (14). This recommendation is based partly on the recognition that these patients have many of the same risk factors—namely, immobilization, heart failure, obesity, and acute severe illness—as patients in whom prophylaxis is shown to have been valuable. The relatively low incidence of DVT found by venography or fibrinogen scanning (12,13) has led some authors to advise caution or suggest the use of heparin only in cases where DVT is demonstrated.

One study (11) compared the number of emboli in patients with respiratory failure (of whom 40% were COPD patients in hypercapnic respiratory failure) given prophylaxis with matched historical controls not given low-dose heparin prophylaxis. Emboli demonstrated by angiography or autopsy or high-probability lung scan occurred in 13 of 98 control cases, but in only 2 of 99 cases during the period of regular prophylaxis, even though 21 of 99 were not given heparin because of contraindications to anticoagulation. There was no increase in frequency of bleeding complications in the year when routine prophylaxis was given.

### B. Treatment

Once thromboembolism has been diagnosed, the treatment is the same as for other patients with this condition and consists of heparin intravenously in a dose to increase the activated partial thromboplastin time to 1.5–2 times control. This is continued for 10 days while oral anticoagulation is begun on the third day and adjusted to produce an INR between 2 and 3. In COPD patients with right heart failure, the long-term use of oral anticoagulants is often made more difficult by variations in liver function due to congestion. Fibrinolytic therapy may be considered when there is hemodynamic instability. The reduced reserve of the patient with COPD, who may be especially vulnerable to the effects of further emboli, makes an additional argument in favor of fibrinolysis. As in other conditions, there are as yet no outcome trials demonstrating that the advantages of thrombolytic treatment outweigh the risks.

### C. Management Based on Leg Tests

In patients without cardiorespiratory disease, a series of recent studies has shown that diagnosis of pulmonary embolism per se is not necessary to make the clinical decision to anticoagulate or not. Instead, a diagnostic test (either impedance plethysmography or Doppler ultrasound) that identifies thrombi in the veins of the leg above the knee can be done. Outcome trials show that if these tests are negative and remain negative for 2 weeks, anticoagulation is not necessary, because no ill consequences are likely to result in months of follow-up (15). The conclusions of these studies cannot be extended with confidence to COPD patients, however. The leg tests are more difficult to do and less accurate in sick patients with high venous pressure. The specificity of IPG and Doppler ultrasound in decompensated COPD patients was as low as 25 and 33%, respectively (13). Also, the importance of in situ thrombosis or of emboli arising from thrombi in the right ventricle and the possibility that these could be prevented by anticoagulation have not been tested. Finally, outcome trials in which the successful endpoint is many symptom-free months in follow-up could overlook the occurrence of small emboli that cause no noticeable disturbance in subjects with normal lungs but could be important to patients with advanced COPD. Outcome trials have not been done in COPD patients.

### D. Decision Making

In clinical medicine the issue is always to make the best intervention. Usually—especially in the setting of severe complex problems such as acute respiratory failure in COPD—decisions must be made on the basis of incomplete information and incomplete understanding of pathophysiology. The linear logic that requires establishment of a certain diagnosis before administering a treatment cannot often

be applied. Chapter 33 shows how the logic of decision analysis permits the physician to use known probabilities to calculate the course of action most likely to benefit a patient with suspected thrombolism in COPD in ARF.

## IV. Pathophysiology

### A. Hemodynamic Effects

There are essentially no reports that describe the very acute changes in hemodynamics provoked by thromboembolism in patients with COPD. Studies in animals give evidence about possible effects and mechanisms. Studies in patients who were normal beforehand show the state of the cardiovascular system hours to days after embolism (16). Similar studies after the event in patients with previous cardiorespiratory disease give some hint about what may happen in COPD (17,18).

#### *Animal Experiments*

Experimental studies of acute obstruction of the pulmonary vascular bed in animals give a picture of a complex set of interacting events. With thromboembolism occluding a major portion of the vascular bed, pulmonary artery pressure and right ventricular pressure rise immediately to very high levels (peak right ventricular pressure of more than 50 systolic, increasing to 80 systolic with volume loading) and then subside over minutes to a somewhat lower value (19). Cardiac output falls and right-side filling pressure increases.

Several factors can contribute to the fall in cardiac output. These may be most logically analyzed by focusing on mechanisms that determine stroke volume of the left ventricle. In a patient without preexisting coronary artery disease, there is no reason to expect embolism to cause ischemia of the left ventricular myocardium or a change in left ventricular myocardial contractility. Left ventricular preload is therefore the central focus of current analyses. It is important to emphasize that preload must be defined in terms of end-diastolic volume of the left ventricle (LVEDV) rather than intracavitary end-diastolic pressure (LVEDP). It is now clearly recognized that the relationship between intracavitary LVEDP and LVEDV may not be predictable in pulmonary embolism. In fact, in contrast to the usual diastolic pressure-volume relationship, in embolism an increase in intracavitary LVEDP may be associated with a decrease in LVEDV. However, transmural LVEDP does have a predictable relationship with LVEDV in embolism, as in other circumstances. Transmural pressure for the left ventricle can be calculated as intracavitary pressure minus pericardial pressure. In acute embolism, distension of the right atrium and right ventricle cause increased pericardial pressure, which creates a situation in which intracavitary pressure is not the true distending pressure.

One factor in reduction of FLEDV is a decrease in output of the right ventricle. The first reason for reduction in output of the right ventricle is simply the mechanical effect of a large increase in afterload on that ventricle. With embolism, pulmonary vascular resistance and pulmonary artery pressure suddenly rise. As a result, stroke volume and cardiac output of the right ventricle are reduced. Flow through the pulmonary circuit and into the left ventricle is reduced. The low output of the left ventricle is thus due in part to inability of the right ventricle to supply enough flow to fill the left ventricle in diastole. This is the "series" mechanism for reduction in LVEDV.

Another reason for reduction in right ventricular output is relative ischemia of the right ventricular myocardium. With embolism, right ventricular intracavitary pressure during systole is greatly increased, and the oxygen requirement of the right ventricular myocardium increases. At the same time, coronary artery perfusion pressure (equal to aortic pressure minus RV intracavitary pressure) is decreased. Coronary artery blood flow to the right ventricle therefore fails to increase enough to match the demand. Insufficiency of coronary blood flow may then contribute to a decrease in right ventricular contractility (20–24). In acute pulmonary embolism in dogs, cardiac output can actually be increased by placing a constricting band around the aorta or giving phenylephrine, at least in part, because this raises coronary perfusion pressure to the right ventricle (25,26). In the maneuver, the negative effect of the increase in afterload on the left ventricle is less important than the benefit of the increase in perfusion of the right ventricle, which results in an increase in the right ventricle's ability to generate pressure to overcome the high pulmonary vascular resistance. The second major factor in reduction of LVEDV is ventricular interaction. With embolism, right ventricular filling pressure rises while LVEDP remains the same or falls. The lower or negative end-diastolic transseptal pressure gradient causes the septum to shift toward the left. The relatively indistensible pericardium prevents the left ventricular free wall from moving outward. The left ventricular cavity is thus constrained from expanding in diastole by two eternal factors, the pericardium and the right ventricle. For a given LVEDP, LVEDV is lower and stroke volume is reduced by the Frank-Starling law. Two observations from dog experiments support the importance of this mechanism. Following acute embolism, dogs can have their stroke volume and cardiac output reduced further by raising right-side venous pressure by volume loading; subsequent removal of blood causes a reversal of this effect. The decrease and subsequent increase in output are directly related to both LV transmural pressure and LVEDV. Volume loading causes both parameters to decrease, and removal of blood causes both of them to increase (27). Second, in dogs who have had their pericardium removed, it is more difficult to cause hypotension by means of embolization (28). In the absence of the pericardium, volume loading and removal of blood have effects opposite to the effects when the pericardium is intact.

Recent evidence has shown that, in the presence of a large right ventricular afterload, the increase in cardiac output that occurs with an increase in left ventricular afterload is not solely due to improved perfusion of the right ventricular myocardium, but is partly due to altered ventricular interaction. Dogs with constriction applied to the pulmonary artery had their coronary artery flow controlled by cannulating the right coronary artery and driving flow with a perfusion pump. While coronary pressure was either maintained at control levels or increased to equal mean aortic pressure during aortic constriction, aortic constriction caused a shift of the interventricular septum back towards the right ventricle, with an increase in left ventricular end-diastolic volume and right ventricular stroke output. While the mechanism is not completely understood, there is clearly a change in function of the ventricular septum associated with the improvement (I. Belenkie et al. personal communication).

### *Observations in Humans*

The data in humans have been reviewed up to 1984 (18) and can be summarized as follows. In previously normal subjects, emboli that occlude less than 50% of the vascular bed have little detectable effect. The greater the portion of the vascular bed occluded, the greater the degree of rise in pulmonary vascular resistance, of fall in cardiac output, and of rise in pulmonary artery and right ventricular end-diastolic pressure. The mean pressure generated by a previously normal right ventricle is not much above 40 mmHg when measured some time after even a massive embolism. When right ventricular filling pressures are very high, the ventricular septum is usually shifted to the left (29), where it could limit left ventricular diastolic volume and reduce cardiac output by the mechanisms detailed above. Under these circumstances in animals, volume loading can precipitate shock, whereas subsequent phlebotomy or systemic vasoconstriction can improve cardiac output, but there is only anecdotal evidence to suggest that these maneuvers might have the same effect in some human patients.

Some clinical reports have suggested that pulmonary emboli can cause pulmonary edema. There is no suggestion from animal studies that embolism causes an increase in LVEDP, however, and good documentation in humans of pulmonary edema due to pulmonary embolism is unavailable.

In acute respiratory failure due to COPD it is possible to speculate that the hemodynamic effects would be somewhat different in magnitude from those in normal subjects. In patients with previous cardiorespiratory disease, pulmonary artery pressure and pulmonary vascular resistance were found to be much higher than in previously normal subjects with pulmonary emboli and were not correlated with the degree of pulmonary vascular occlusion (18,30). These patients, including some with COPD, presumably had longstanding pulmonary hypertension, and many had right ventricular hypertrophy.

Patients with COPD have higher pulmonary vascular resistance and less ability to increase pulmonary flow with an increase in pulmonary artery pressure. With the same amount of embolic obliteration of pulmonary vascular cross-sectional area, it could be expected they would have a greater increase in pulmonary vascular resistance than a previously normal person. The effect of a sudden change in pulmonary vascular resistance is an increase in pulmonary artery pressure, in right ventricular filling pressure, and therefore in venous pressure. Cardiac output might tend to decrease more than in a normal person because a given rise in pulmonary artery pressure would be less able than normal to restore cardiac output toward normal. On the other hand, a hypertrophied right ventricle can probably increase PA pressure more than a normal right ventricle.

As in animals, a very high right ventricular end-diastolic pressure (RVEDP) (and therefore a reversal of the normal transeptal pressure gradient) in humans tends to push the septum to the left, reducing left ventricular end-diastolic volume and thus reducing cardiac output. In a patient with a previously high right-sided pressure, a given embolus of a certain size would be more likely to cause a rise in RVEDP great enough to reverse the transeptal pressure gradient. In fact, some patients with COPD, cor pulmonale, and fluid retention in acute respiratory failure have been found to have reached this state, where diuresis by lowering RVEDP can restore the normal transeptal gradient and could increase LV stoke output and cardiac output (31). The same effect can be seen in some experimental animals with previously normal hearts, acute pulmonary emboli, and severe hemodynamic compromise. It is plausible to suppose that this scenario could arise in some COPD patients with sizable emboli, especially if they previously had high right-side filling pressures.

Finally, embolism can produce bronchoconstriction in normal subjects. To the extent it does so in COPD patients, it will increase pulmonary resistance, and therefore intrinsic PEEP. In patients on positive pressure ventilation, this will increase mean intrathoracic pressure and may have a detrimental hemodynamic effect, both by reducing venous return and by constraining left ventricular filling.

In conclusion, one might expect smaller emboli to have greater hemodynamic effects in COPD compared to people with normal lungs and hearts. The effects of embolism on hemodynamics are complex and still incompletely understood. The data from experimental studies of emboli in previously normal anaesthetized animals suggest that, when intramuscular volume is high, cardiac output could be improved by either decreasing volume or giving systemic vasoconstrictors. This would be especially likely if the interventricular septum were found moving paradoxically in systole, as this finding is associated with LV diastolic constraint caused by high right-side pressures. At this time, however, there is very little data in humans to help predict under what conditions of pressure, resistance, cardiac output, or observed septal motion these maneuvers would likely be

helpful. Clinical studies are needed in which these concepts are tested by means of comprehensive hemodynamic measurements.

### B. Gas-Exchange Effects

The effects of pulmonary emboli on gas exchange are quite well described in subjects with previously normal lungs. In COPD it is reasonable to expect that the effects of emboli on gas exchange might be more substantial than in normal subjects.

*1. Part of the pulmonary vascular bed is obliterated.* This causes some shift of $\dot{V}_A/Q$ ratios to higher values and an increase in dead-space. Dead-space and alveolar arterial difference in $P_{CO_2}$ are already increased by the underlying COPD. Any further increase in dead-space will have a more marked effect on arterial $P_{CO_2}$ than in normal subjects. There are two reasons for this. First, the arithmetic relating $P_{CO_2}$ to dead space:

$$Pa_{CO_2} = k\frac{\dot{V}_{CO_2}}{\dot{V}_E(1 - VD/VT)}$$

implies that when VD is large, as is the case in COPD, the denominator $\dot{V}_E$ $(1 - VD/VT)$ is small, and any given change in the denominator then has a more important effect on the quotient, $Pa_{CO_2}$. This effect may be aggravated because the COPD patient has very limited capacity to increase $V_T$ to try to maintain the $V_D/V_T$ ratio. Second, normal subjects with acute pulmonary emboli have a large ventilatory reserve and tend to hyperventilate when stimulated by hypoxemia or other effects of embolism. COPD patients in acute respiratory failure are less able to do this. When $V_D/V_T$ changes, therefore, $P_{CO_2}$ may fall less than in normal subjects or may actually rise (3).

*2. Bronchoconstriction occurs not only in the embolized zone but in other regions as well, causing a shift of $\dot{V}/\dot{Q}$ ratios to lower values.* Bronchoconstriction in COPD following embolization may or may not be as brisk as in normal subjects. Because of the small caliber of airways initially, however, any constrictive action will have a disproportionate effect on resistance, and therefore on the time constants of affected units. The dispersion in $\dot{V}_A/\dot{Q}$ ratios induced by this mechanism could easily be more important than in normal lungs. Widespread bronchoconstriction in patients with little respiratory muscle reserve could also result in a decrease in alveolar ventilation and a rise in $P_{CO_2}$.

*3. Some pulmonary edema may occur.* This may be due in part to a fluid leak. Although never conclusively demonstrated, a rise in LVEDP might also occur in some patients, particularly those with preexisting left ventricular ischemic disease. High LVEDP pulmonary edema causes areas of low $\dot{V}_A/\dot{Q}$, partly by squeezing airways contained in connective tissue sheaths, partly through submucosal edema in airways, and partly by inducing bronchial hyperreactivity.

As above, airways that are already small will be affected much more than normal ones. An example of this is given by mild volume loading of patients with COPD in ARF, which has much more marked effects on gas exchange than in normal subjects (32).

*4. Intrapulmonary shunting occurs, perhaps due to atelectasis, haemorrhage, and edema.* The degree of hypoxemia induced by shunting and $\dot{V}_A/\dot{Q}$ disturbances is likely to be greater in COPD than normals. It has recently been shown that the main factor determining hypoxemia in normal subjects with pulmonary emboli is a drop in mixed venous oxygen tension (33–35). This interacts with the venous admixture to lower the arterial $P_{O_2}$. In COPD, as above, one may expect more dramatic hemodynamic effects, with lower cardiac output in combination with preexisting low arterial $P_{O_2}$ promoting lower mixed venous $P_{O_2}$.

*5. In persons with a patent foramen ovale*, the possibility exists of an increase in right-to-left shunting within the heart because of the rise in right-sided pressures.

## V. Summary

The problem of thromboembolism, and of in situ thrombosis of pulmonary arteries in COPD remains difficult to study and to assess in the individual patient. Mechanisms for hemodynamic changes and alteration in gas exchange in normal lungs have been well described in animal models and some human experiments. It can be argued on theoretical grounds that these pathophysiological consequences of emboli would be more severe in patients with underlying COPD. Short of performing angiography on all patients, accurate means for diagnosis of acute pulmonary embolism in COPD have not been established, and the incidence in COPD is not reliably known. There are a few reliable clinical indicators to select patients in whom the likelihood of embolus is great enough to justify angiography, but the arterial end-tidal $CO_2$ gradient shows promise in this regard. Experimental evidence suggests that hemodynamic collapse in acute embolism may be prevented in certain cases by reducing vascular volume or by systemic vasoconstriction. These concepts need to be tested clinically.

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# 15

# Left Ventricular Function During Acute Respiratory Failure of Chronic Obstructive Pulmonary Disease

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## I. Introduction

The relationships between chronic obstructive pulmonary disease (COPD) and left ventricular (LV) dysfunction (and/or hypertrophy) have been the subject of debate for several decades. Due to improved techniques of LV function assessment, this subject has recently been clarified (1,2).

Many studies demonstrated in the past the high prevalence of LV hypertrophy in patients with known COPD, with or without cor pulmonale, as reviewed recently by Wise (2). Typically, in 1966, Fluck et al. (3) carried out a retrospective postmortem study in patients with chronic bronchitis measuring the thickness of left and right ventricular walls. They found that LV wall thickness was increased ($\geq$17 mm) in 25% of the chronic bronchitis patients and in only 7% of the controls. However, the elimination of patients with independent LV disease—mostly ischemic—which could at least partly explain their findings, was not very carefully done. Later, Murphy et al. (4) conducted a prospective pathological study paying more attention to finding a specific cause for LV involvement (e.g., they performed postmortem angiograms). Twenty-eight percent of their 72 patients with chronic bronchitis had LV hypertrophy, but hypertensive cardiovascu-

lar disease explained most of it. Kachel (1), reviewing the available literature on this subject in 1978, came to the conclusion that a significant percentage of patients with COPD have coronary artery disease (CAD), and once CAD is specifically excluded the majority of COPD patients have a normal LV function. Wise (2) reviewed the literature of the past two decades, concerned with LV dysfunction in patients with COPD. His conclusion was that the prevalence of unexplained LV dysfunction appears to be most closely related to the methodology used and to the diligence of seeking out occult CAD, alcoholism, or valvular heart disease (2).

Although LV function is normal in patients with a pure COPD, the coexistence of COPD and LV disease related to CAD, hypertension, or alcoholism is relatively frequent (1,5). This may lead to difficulties in establishing diagnosis and subsequent therapeutic strategies in patients with both diseases suffering from an acute respiratory failure. Furthermore, an acute LV dysfunction may worsen the severity of the acute exacerbation of COPD and vice versa.

In this chapter, we will not extensively discuss the role of the LV dysfunction in the aggravation of the symptoms of an acute exacerbation of COPD. Briefly, the mechanisms are clear and mostly related to the increased airway resistance due to the peribronchial localization of the edema. We will rather focus on the possibility that an acute exacerbation might trigger an acute episode of cardiogenic pulmonary edema (CPE) in patients chronically suffering from both COPD and LV disease. We will describe later a clinically relevant application of such deleterious heart lung interactions—the onset of a weaning-induced acute LV dysfunction, explaining some cases of weaning failure.

## II. Respiratory Characteristics of Acute Exacerbation of COPD Potentially Involved in Acute LV Dysfunction

Lung hyperinflation, markedly negative intrathoracic pressure, increased abdominal pressure, hypoxemia, and hypercapnia are five major characteristics of acute exacerbation of COPD, which may act to precipitate LV dysfunction and CPE formation in a patient with preexisting LV disease.

### A. Lung Hyperinflation

Lung hyperinflation is the consequence of two mechanisms: (1) the reduced elastic recoil pressure in emphysema which results in an increased relaxation volume, and (2) the dynamic pulmonary hyperinflation phenomenon, favored by increased airway resistance, decreased elastic recoil pressure, tachypnea and mainly expiratory airflow limitation. This results in an end-expiratory lung volume higher than the relaxation volume and a positive static end-expiratory elastic recoil pressure called intrinsic PEEP. Intrinsic PEEP present in stable COPD (6)

further increases during acute exacerbation (2). Intrinsic PEEP represents a significant inspiratory threshold load, resulting in a marked negative swing in intrathoracic pressure during inspiration and an increased work of breathing.

### B. Negative Intrathoracic Pressure

The intrathoracic pressure may be markedly negative in inspiration during acute exacerbation of COPD because of (1) increased airway resistance and (2) increased lung volume. Inspiratory airway resistance is increased during acute exacerbation of COPD (7). It normally leads to a more negative intrathoracic pressure in inspiration to generate a sufficient tidal volume. Breathing at high lung volume results in a shift of the respiratory system toward the less compliant portion of the pressure-volume relationship so that intrathoracic pressure must be increased in absolute value to generate a sufficient tidal volume.

### C. Increased Abdominal Pressure

During spontaneous inspiration in the supine position, the abdominal pressure increases because of the lowering of the diaphragm (8,9). One concern in patients with COPD is that the increased functional residual capacity might lead to a marked rise abdominal pressure with inspiration because of the diaphragmatic descent. In fact, the diaphragm may no longer be the major inspiratory agonist in hyperinflated patients (10). Murciano et al. (11) showed that in the great majority of patients with acute exacerbation of COPD, there was little or no change in gastric pressure during spontaneous ventilation. In this situation, the diaphragm acts essentially as a fixator (10).

### D. Hypoxemia

This is a common feature in stable COPD. It constantly worsens during acute exacerbation mainly because of ventilation-perfusion mismatching (10,12–14).

### E. Hypercapnia

Hypercapnia commonly occurs in acute exacerbations of COPD. Its pathogenesis and implications are discussed in details in other chapters of this book.

## III. Mechanisms of Potential LV Dysfunction During Acute Exacerbations of COPD

LV dysfunction and CPE may occur during acute exacerbation of COPD because of the decrease in LV compliance, the decrease in LV contractility, or the increase in LV afterload.

### A. Decrease in LV Compliance

At least four mechanisms can potentially reduce LV compliance during acute exacerbations of COPD.

#### *Biventricular Interdependence*

The two ventricles share the septum as a common wall; the expansion of one ventricle within a relatively indistensible pericardium limits the filling of the other ventricle in diastole (15,16). Two factors may contribute to increased right ventricular (RV) end-diastolic volume during acute exacerbation of COPD: increased systemic venous return and increased RV afterload.

##### Increased Systemic Venous Return

*Effects of Changes in Intrathoracic Pressure on Venous Return.* During acute exacerbation of COPD, the marked inspiratory decrease in intrathoracic pressure results in a substantial decrease in mean intrathoracic pressure. This leads to a decrease in right atrial pressure relative to atmosphere, enhancing the pressure gradient available to promote venous return. This phenomenon has a counterpart, however: if right atrial pressure decreases below the atmospheric pressure, the systemic veins collapse as they enter the thorax, thus limiting blood flow (17).

*Effects of Abdominal Pressure on Venous Return.* The effects of abdominal pressure on venous return depend upon the intravascular volume status (9,18, 19). Takata et al. (19) proposed the concept of abdominal vascular zone conditions analogous to pulmonary vascular zone conditions. In this connection, when the intravascular status is low, the increased abdominal pressure may collapse the vena cava and cause blood flow limitation from the lower extremities and hence a decrease in systemic venous return from the interior vena cava. When the intravascular volume is high, no critical closure pressure occurs since the pressure surrounding the inferior vena cava does not exceed the intraluminal pressure; in this condition, the increased abdominal pressure raises the gradient for systemic venous return and induces a net increase in venous return from the inferior vena cava leading to an increased right atrial pressure. Thus, the net effect of increased abdominal pressure in presence of normo- or hypervolemia is an increased systemic venous return.

*Effects of Lung Inflation on Venous Return.* As discussed above, lung hyperinflation occurs in COPD, especially during acute exacerbation. Increases in lung volume may directly impede systemic venous return through either compression of the vena cava (20) or direct mechanical compression of the right heart (21). This requires intrapleural pressure to be positive and is among the consequences of intrinsic PEEP. It remains to be demonstrated whether these mechanisms actually play a role with spontaneous inspiration during acute exacerbation of COPD.

*Effects of Hypercapnia on Venous Return.* It is likely that hypercapnia and respiratory acidosis increase venous return (22) by increasing circulating catecholamine (23).

In summary, systemic venous return normally increases during acute exacerbation of COPD. However, exaggerated inspiratory efforts with marked drops in intrathoracic pressure may be associated with reduction in venous return because of flow limitation of the vena cava, increased abdominal pressure, and lung hyperinflation, especially when intravascular volume is low. Such events could occur also in patients with acute asthma, another clinical condition with increased airway obstruction, increased lung volume, and marked inspiratory drop in intrathoracic pressure (24). In this connection, Squara et al. (25) reported in asthmatic patients a reduction in the degree of pulsus paradoxus when central blood volume was increased after inflating the medical antishock trousers.

### Increase in RV Afterload

COPD is associated with destruction of the pulmonary vascular bed and hypoxemia, both of which result in pulmonary hypertension. During acute exacerbation of COPD, pulmonary hypertension (10) is aggravated for several reasons: (1) further reduction in $Pao_2$, which always occurs (10), (2) respiratory acidosis, which acts in association with hypoxemia to further increase pulmonary vascular resistance (26), and (3) aggravated lung hyperinflation. Pulmonary vascular resistance is normally minimal at a level of lung volume near to relaxation volume (27). During acute exacerbation of COPD, the patient breathes at high lung volume since the end-expiratory lung volume is significantly higher than the relaxation volume, as discussed earlier. Although such lung hyperinflation results in a decreased resistance of extraalveolar pulmonary vessels, the increased resistance of intraalveolar pulmonary vessels will result in a net effect of increased pulmonary vascular resistance (27).

Markedly negative intrathoracic pressure at inspiration may also impede RV afterload. Indeed, the pressure surrounding the right ventricle decreases while the pressure surrounding the intraalveolar vessels is close to atmospheric pressure at end-inspiration. Therefore, the right ventricle, which must pump blood over the wall out into the alveolar arterial bed, has to generate a higher pressure (i.e., transmural pressure) before blood can reach alveolar vessels. In other words, the right ventricle senses this condition as an increased impedance to its ejection (i.e., an increase in its afterload) (28). In fact, this phenomenon is only transient because at the same time, the increased driving pressure between the alveolar vessels and the left atrium (because the left atrium is surrounded by a negative intrathoracic pressure) facilitates blood flow from alveolar vessels to the left atrium and thus results in a reduction in blood volume and pressure in the alveolar vessels until the initial pressure is restored in this new steady state (29).

Only a few studies have examined the effects of acute exacerbation of

COPD on RV dimensions. Settle et al. (30) reported increased inspiratory RV dimensions measured with echocardiography in 9 patients with COPD and pulsus paradoxus. Using two-dimensional echocardiography, Jardin et al. (31) observed increased RV end-diastolic and end-systolic dimensions in 10 patients with mild acute exacerbation of COPD when compared with a group of 12 normal volunteers.

Increased RV volumes during inspiration could result in decreased LV compliance and preload and increased LV filling pressure (15,16,32). During loaded inspiration in animals (33,34) and inspiration in patients with acute asthma (24), some authors reported increased RV dimensions associated with decreased LV end-diastolic volume and LV stroke volume consistent with a biventricular interdependence mechanism. Simultaneous measurements of increased transmural LV filling pressure with inspiration strongly suggested a reduced compliance of the left ventricle in this condition (24,33,34).

During a Mueller maneuver in normal men, Brinkler et al. (35), using two-dimensional echocardiography, demonstrated that increased RV dimensions resulted in an acute leftward septal displacement and decreased LV end-diastolic dimensions. In patients with stable COPD, Settle et al. (30) reported that inspiration was associated with RV enlargement and decreased LV dimensions consistent with a biventricular interdependence phenomenon. During acute exacerbation of COPD, Jardin et al. (31), using two-dimensional echocardiography, observed septal flattening both at end-diastole and end-systole, associated with increased RV dimensions and decreased LV dimensions and stroke volume when compared to those measured in normal volunteers.

Therefore, many arguments suggest that during acute exacerbation of COPD, because of the dilation of the right ventricle at least during inspiration, the compliance of the left ventricle could be decreased. This normally leads to reduced LV preload and increased LV filling pressure. However, it remains unknown whether this mechanisms alone can promote CPE in a patient with COPD.

### *Direct Compression of the Left Ventricle by Hyperinflated Lungs*

Increased lung volume in a patient with COPD may exert cardiocirculatory effects not only through changes in intrathoracic pressure or through direct compression of the vena cava or the right ventricle, but also through a direct compression of the left ventricle. A shape change in the left ventricle might occur when compressive forces associated with lung inflation are applied in a nonuniform manner over the surface of the heart (36).

Some authors reported that during PEEP ventilation, pericardial and mediastinal pressures increase more than esophageal or lateral intrathoracic pressure and attributed this to compression of the heart by the inflating lung (37–39), which

in turn decreases LV septal-lateral dimensions (40–42). During spontaneous inspiration, decreases in the LV septal-lateral dimensions consistent with compression of the heart in the lateral direction were also reported (43–45). Robotham et al. (43) observed that such septal-lateral dimensions decrease only when lung volume was allowed to increase. However, Scharf et al. (45) failed to find a significant difference in the change of different regional LV surface pressures during spontaneous inspiration and concluded that the compressive effect of lung inflation probably plays a less important role during spontaneous inspiration than during mechanical ventilation with PEEP.

Still, Butler's studies of patients with COPD reported rises in wedge pressure on exercise, explained not by increased esophagal pressure but rather by increased juxtacardiac pressures produced by exercise-induced air trapping (46–48) (Fig. 1). Although in patients with acute exacerbation of COPD the importance of a direct compressive effect of lung distension is not clearly established, one may at least postulate that lung hyperinflation by external cardiac filling restriction might enhance the degree of ventricular interdependence.

### *Myocardial Ischemia*

In a patient with a preexisting CAD, an acute exacerbation of COPD has the potential for inducing some degree of myocardial ischemia through several mechanisms.

#### Myocardial $O_2$ Demand Might Be Potentially Increased

The increased work of breathing results in an increased $O_2$ cost of breathing (49), which must lead to an increased cardiac work to ensure an adequate $O_2$ delivery to respiratory muscles. This results in an increased myocardial $O_2$ demand.

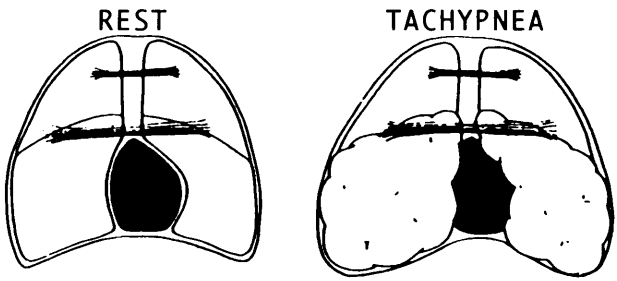


**Figure 1** Effects on the heart of lower lobe distension due to gas trapping. The pleural surfaces of the cardiac fossa become tense as the lungs which are bound together by the hilar structure and pulmonary ligaments, inflate. (From Ref. 47.)

As we will discuss later, the potential increase in LV afterload during loaded inspiration may lead to increased systolic LV wall stress and hence myocardial $O_2$ demand.

#### Myocardial $O_2$ Delivery Might Be Potentially Reduced

The further reduction in $Pao_2$ combined with respiratory acidosis may lead to very low values of $Sao_2$, which may significantly lower the amount of $O_2$ delivered to myocardium.

The decrease in diastolic arterial pressure related to the decrease in intrathoracic pressure during inspiration may be significant in patients with a high degree of pulsus paradoxus. As diastolic arterial pressure is the inflow pressure to coronary perfusion, a decrease in coronary blood flow could occur. Scharf et al. (51) measured reduced coronary blood flow at inspiration compared with end-expiration in anesthetized vagotomized dogs breathing against an inspiratory threshold load. It is of note that the decrease in coronary blood flow paralleled the changes in arterial pressure over the respiratory cycle (50).

The increased $O_2$ cost of breathing required an elevated $O_2$ delivery to the respiratory muscles. This is usually provided by augmentation of cardiac output and blood flow redistribution toward respiratory muscles (51). When the augmentation of cardiac output is limited because of a failed heart, the degree of blood flow redistribution increases, which may lead to some degree of ischemia in other organs. Although the coronary circulation is relatively protected in this condition, one might speculate that in a patient with obstructed coronary vessels, this could result in a significant myocardial ischemia.

Despite these theoretical arguments, no evidence of myocardial ischemia during acute exacerbation of COPD in patients with preexisting CAD is found in the literature. However, pertinent data were reported by Scharf et al. (52) studying the effects of a Mueller maneuver (with decrease in intrathoracic pressure to $-20$ to $-30$ $cmH_2O$) in subjects with or without CAD. They found that 9 of 14 patients with CAD showed the development of LV wall akinesis, whereas none of the 17 subjects without CAD exhibited regional akinesis during the Mueller maneuver. In a subsequent study, Scharf et al. (53) demonstrated that prior transmural myocardial infarction was a necessary condition for the development of regional wall akinesis during the Mueller maneuver in patients with CAD. Thus the Mueller maneuver increases the sensitivity for detecting areas of motion abnormalities, which probably represent areas of prior myocardial infarction.

### *Effects of Acute Severe Hypoxemia*

Independent of its potential deleterious effects in patients with CAD, acute hypoxemia could reduce LV compliance even in patients with normal left heart by producing an increase in wall thickness, which is in part attributed to greater coronary blood flow resulting in myocardial tumescence (54).

### B. Decrease in LV Contractility

There is no direct argument suggesting a decrease in LV contractility during acute exacerbation of COPD. Nevertheless, indirect arguments should be mentioned.

#### *Myocardial Ischemia*

A potential induction of some degree of myocardial ischemia in a patient with CAD is a theoretical factor that could result in a reduction in contractility.

#### *Respiratory Acidosis*

A marked respiratory acidosis with high levels of hypercapnia can decrease LV contractility. In a whole-animal preparation, Walley et al. (22) found that respiratory acidosis (pH = 7.09 ± 0.04; $P_{CO_2}$ = 92 ± 9 mmHg) directly decreases LV contractility in accord with excised heart studies (55). The authors analyzed the end-systolic pressure-volume relationship as a relative preload- and afterload-insensitive index of contractility (22). When the β-receptor response was blocked by propranolol, the induction of respiratory acidosis resulted in a further reduction in contractility (Fig. 2), suggesting that the adrenergic response to respiratory acidosis attenuates some of the direct reduction of contractility but does not completely prevent it (22).

#### *Hypoxemia*

A progressive hypoxemia induced in a whole-animal preparation was also demonstrated by the same group of investigators to decrease LV contractility assessed by end-systolic pressure-volume relationship (56).

### C. Increase in LV Afterload

#### *Effects of Negative Intrathoracic Pressure*

During an inspiratory effort, the pressure surrounding the left ventricle decreases while the pressure surrounding the extrathoracic arterial compartment remains constant. As the left ventricle must pump blood over the wall out into the extrathoracic arteries, it must generate a higher pressure (i.e., transmural pressure) before blood can leave the thorax. In other words, lowering intrathoracic pressure would be equivalent to raising the arterial pressure by a similar amount, and both conditions will be sensed as an increased afterload to the left ventricle (28,57–59). In animal experiments, many reports of increased transmural LV systolic or aortic pressure with decreased intrathoracic pressure have supported the conceptual hypothesis of increased LV afterload during inspiration (33,34,57,60,61). In human studies, increased aortic transmural pressures were also measured during Mueller maneuver in normal volunteers (62) or in cardiac surgery patients (63). In

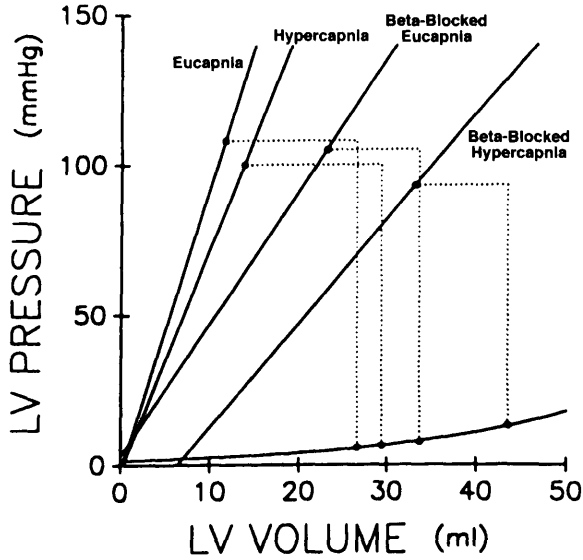


**Figure 2** Left ventricular (LV) pressure-volume relationships for four experimental conditions in dogs. Eucapnia and hypercapnia before and after beta-blockade (see text for comments). (From Ref. 22.)

patients with COPD breathing in experimental conditions where inspiration and expiration were loaded (conditions simulating acute exacerbation), Viola et al. (64) also demonstrated increased transmural arterial pressure with inspiration, consistent with increased LV afterload. More consistent with this hypothesis was the observation during Mueller maneuver of simultaneous increases in transmural pressure and in end-systolic and end-diastolic LV volumes measured either by radionuclide ventriculography in normal volunteers (52,62) and in patients with CAD (62) or by cinefluorography of implanted radioopaque markers in cardiac surgery patients (63). During loaded inspiration in healthy subjects undergoing radionuclide ventriculography, Karam et al. (65) also concluded that negative intrathoracic pressure may cause an impediment to LV ejection after observing increases in LV end-systolic counts and decreases in stroke counts and ejection fraction.

However, it must be remembered that Brinkler et al. (35) measured with two-dimensional echocardiography reduced end-systolic and end-diastolic LV sizes during Mueller maneuver in normal men. With a similar technique, Jardin et al. (24) also measured decreased LV dimensions during deep inspiration in patients with acute asthma. Methodological differences in determining ventricular volumes and/or differences in the maximal inspiratory negative intrathoracic

pressure probably account at least partly for the discrepancies in ventricular chamber sizes among studies.

The problem of changes in LV afterload with intrathoracic pressure was examined in another way by Peters et al. (66). These investigators, to test the hypothesis that negative intrathoracic pressure afterloads the left ventricle, evaluated the effects of a rapid transient decrease of intrathoracic pressure confined to systole with and without changes in lung volume (66). They used intrathoracic descending aortic diameters as a qualitative indicator of afterload, reasoning that aortic diameter should reflect aortic transmural pressure (66). With and without changes in lung volume, systolic negative intrathoracic pressure resulted in a decrease in LV stroke volume but in increased systolic aortic diameters consistent with increased LV afterload (66).

Conflicting results were reported recently by Scharf et al. (50), who, studying phasic effects of inspiratory loading an left ventricular hemodynamics in vagotomized dogs, found that LV transmural pressure decreased during early inspiration secondary to the decrease in stroke volume, which was likely related to a decrease in LV preload. However, they did not exclude an increase in LV afterload with more obstructed inspiration (50). In a series of dog experiments, Peters et al. demonstrated that a decrease in intrathoracic pressure confined to diastole could diminish the ensuing LV stroke volume, presumably reducing preload by biventricular interdependence (67), while a decrease in intrathoracic pressure confined to systole could increase LV afterload (66). These findings underline the difficulty in analyzing cardiopulmonary interactions with respiration and partly explain some divergent results found in the literature. In animal experiments, Robotham et al. (68,69) compared changes in the integrated mitral and ascending aortic blood flow to assess LV inflow and outflow. This allows an estimate of changes in LV end-diastolic and end-systolic volumes independent of any assumption about LV shape. They observed that during spontaneous ventilation, approximately 80% of the time the minimal and maximal integrated mitral flows preceded the respective minimal and maximal integrated aortic flows. This suggests the dominance of preload effects over afterload effects in determining LV output (68,69).

Recently, Takata et al. (70) reported data indicating that the pericardium could modulate the effect of negative intrathoracic pressure on ventricular loading by attenuating increases in both preload and afterload. The authors measured in dogs both intrapericardial surface pressure (Ppe) and esophagal pressure during negative intrathoracic pressure produced by phrenic stimulation (70). They found that Ppe was sensitive to changes in ventricular loading conditions, with end-systolic and end-diastolic values reflecting the changes in ventricular volumes at that instant within a cardiac cycle. In this connection, they demonstrated that during systole Ppe is less negative than esophagal pressure, so that the true surrounding pressure of the ventricles during the ventricular ejection period is less

negative than the imposed negative intrathoracic pressure (70). Thus, the degree of the LV afterload produced by negative intrathoracic pressure is effectively attenuated by the pericardium.

Others (45) also found that intrapericardial pressure actually decreases less than esophagal pressure during inspiratory loading. Thus, there is now some indirect evidence that LV afterload is probably less increased during profound inspiration than it was previously thought.

#### *Effects of Abdominal Pressure*

An increase in abdominal pressure with inspiration during acute exacerbation of COPD, if it actually occurred, would lead to an increased pressure surrounding the abdominal arterial compartment so that the impedance to ejection of the left ventricle would be further augmented (71).

### D. Summary

Because of increased abdominal pressure and marked decrease in intrathoracic pressure, an augmentation of LV afterload is likely to occur with profound inspiration during acute exacerbation of COPD. Although its degree is probably less than previously believed, this may have some consequences in a patient with an associated reduced LV contractility particularly sensitive to changes in LV afterload (72). This concept supports the basis for the use of positive pressure ventilation to improve LV performance in patients with congestive heart failure (72). Pinsky and coworkers demonstrated in a series of studies that generalized increase in intrathoracic pressure was able to improve stroke volume in experimental cardiac failure (74,75) and in human congestive heart failure (76). Moreover, selective increases in intrathoracic pressure during systole further augment LV ejection without decreasing LV preload (77,78).

## IV. Clinical Implications

### A. Acute Exacerbation of COPD

Therefore, it is quite conceivable that in a patient with preexisting LV failure, suffering from acute exacerbation of COPD, there is the potential for an impaired LV ejection and thus elevated LV filling pressure. This, combined with a tendency for increased systemic venous return and for RV enlargement with a subsequent reduction in LV compliance, can result in CPE formation, even if cardiac contractility is not further reduced. In a patient with an associated CAD, as discussed earlier, the phenomenon can be aggravated by a further reduction in LV compliance and/or contractility.

Yet, despite an abundant literature examining the relationships between airway obstruction and cardiac function, there is no clinical study in COPD patients supporting the concept of LV failure and CPE formation during an

authentic acute exacerbation of COPD. Only a few studies showed some evidence of CPE occurrence in the setting of upper airways obstruction (79–81) or acute asthmatic attack (82).

### B. Weaning from Mechanical Ventilation

#### *Conceptual Basis of Weaning-Induced LV Dysfunction*

LV dysfunction and CPE were reported during weaning from mechanical ventilation (MV) in patients with both COPD and LV disease (83). In fact, the transfer from MV to spontaneous breathing can be roughly assimilated to condition of acute exacerbation; although patients are in a better clinical status owing to beneficial effects of MV and resolution of precipitating factors, they have to create a marked negative inspiratory intrathoracic pressure to breathe spontaneously because of an additional inspiratory resistive load imposed by endotracheal tubes (84). In addition, dynamic pulmonary hyperinflation may occur in this setting, because of this supplemental airway resistance, resulting in a still more negative inspiratory intrathoracic pressure, as discussed earlier.

Abdominal pressure is expected to increase with spontaneous inspiration (85). Some degree of hypoxemia and hypercapnia are common during weaning, even when successful, in patients with COPD because of worsening of ventilation-perfusion mismatching (86). Thus, marked negativity of intrathoracic pressure, lung hyperinflation, increased abdominal pressure, hypoxemia, and hypercapnia, which are characteristics of acute exacerbation, can also be present during weaning of COPD patients.

As discussed earlier, these abnormalities have the potential to favor the occurrence of LV dysfunction and CPE, especially in patients with preexisting LV disease (87). In addition, the emotional stress due to the abrupt disconnection from the ventilator in patients ventilated for a long time can result in a dramatic adrenergic response. Lemaire et al. (83) measured a twofold increase in epinephrine and norepinephrine blood levels during weaning of patients with COPD. In addition to emotional stress, marked acute hypoxemia and hypercapnia may contribute to this catecholamine release. Adrenergic discharge could play a role in the induction of LV dysfunction through several mechanisms (87):

Increase in systemic venous return and thus in RV volume (biventricular interdependence)
Increase in systemic arterial pressure and thus in LV afterload
Increase in myocardial $O_2$ demand (tachycardia and increased systolic wall stress (i.e., afterload) potentially deleterious in the setting of CAD

#### *Clinical Studies*

Several studies have examined the consequences of weaning on the left ventricle in patients with COPD. Lemaire et al. (83) suggested that a weaning-induced LV

dysfunction can play a role in preventing successful weaning in patients with COPD and preexisting LV disease. They observed in 15 patients who were recovering from acute cardiopulmonary decompensation that weaning was associated with a dramatic increase in transmural pulmonary artery occlusion pressure (PAOP) from 8 ± 5 to 25 ± 13 mmHg (83).

Some of the patients exhibited large augmentations in LV end-diastolic volume measured by radionuclear angiocardiography (Fig. 3), which may further elevate PAOP by placing the LV end-diastolic pressure on the steeply ascending portion of the LV pressure-volume relationship curve. The augmentation of LV volume in these patients probably resulted from increases in venous return and LV afterload. Increased venous return during weaning was likely in those patients in whom cardiac output was significantly raised; central translocation of blood volume during weaning may result from a marked increase in transdiaphragmatic pressure (i.e., abdominal pressure minus intrathoracic pressure) as underlined by Permutt (85). Many other patients had PAOP increases with minimal augmentation of LV end-diastolic volume (Fig. 3), suggesting reduced LV diastolic compliance. In some patients, this might be related to a ventricular interdependence phenomenon, since they demonstrated large increases in RV end-diastolic vol-

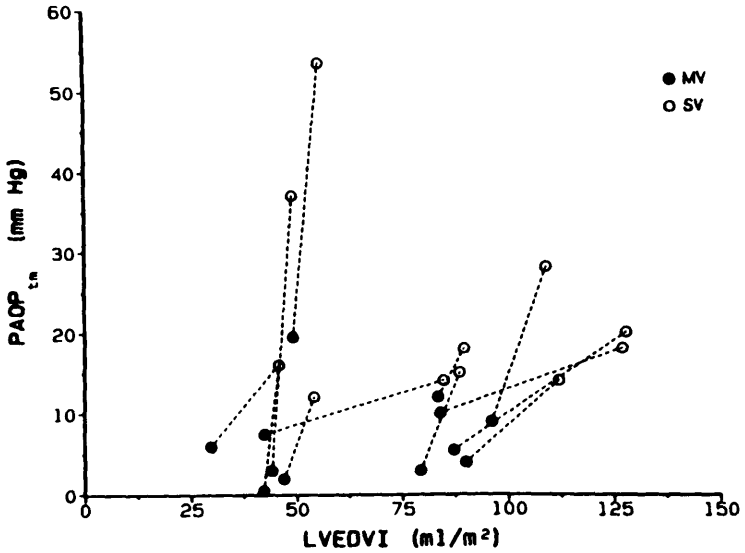


**Figure 3** Changes in transmural pulmonary occlusion pressure ($PAOP_{tm}$) and left ventricular end diastolic volume index (LVEDVI) during the transfer from mechanical ventilation (MV) to spontaneous ventilation (SV) in 12 patients with COPD and preexisting LV disease. (From Ref. 83.)

umes. In three other patients, myocardial ischemia was thought to occur, since they evidenced abnormal LV wall motion during MV which became more severe during spontaneous breathing.

To evaluate the possibility that myocardial ischemia may occur during weaning, Hurford et al. (88) performed a study using Thallium 201 myocardial scintigraphy in 15 ventilator-dependent patients able to spontaneously breathe comfortably for at least 10 minutes. During spontaneous ventilation, 8 of 15 patients exhibited decreased myocardial Thallium uptake with redistribution of the label on delayed images indicating decreased myocardial perfusion (88). In patients with COPD and CAD who failed to wean from MV because of the occurrence of a CPE with increased PAOP, the administration of enoximone, a phosphodiesterase inhibitor, resulted in attenuated rises in PAOP (Fig. 4) and successful weaning (89). In these patients, the marked increase during weaning of the product of heart rate by systolic arterial pressure, regarded as a reflection of myocardial $O_2$ demand, was attenuated after receiving enoximone (89).

More recently, Richard et al. (90) investigated the effects of weaning in 12 patients with COPD but without LV failure or CAD. Using radionuclide angiocardioscintigraphy, they observed significantly decreased LV ejection fraction during weaning (Fig. 5) with unchanged LV end-diastolic volume but increased LV end-systolic volumes (90). These findings were consistent with reduced LV contractility or augmented LV afterload. A reduction in LV contractility was

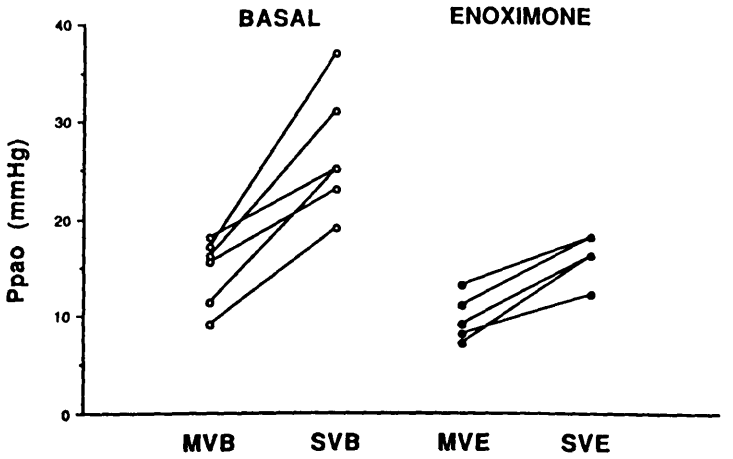


**Figure 4** Changes in pulmonary artery occlusion pressure (Ppao) during the transfer from mechanical ventilation (MV) to spontaneous ventilation (SV) in basal condition (B) and after enoximone administration (E) in six patients with COPD and coronary artery disease.

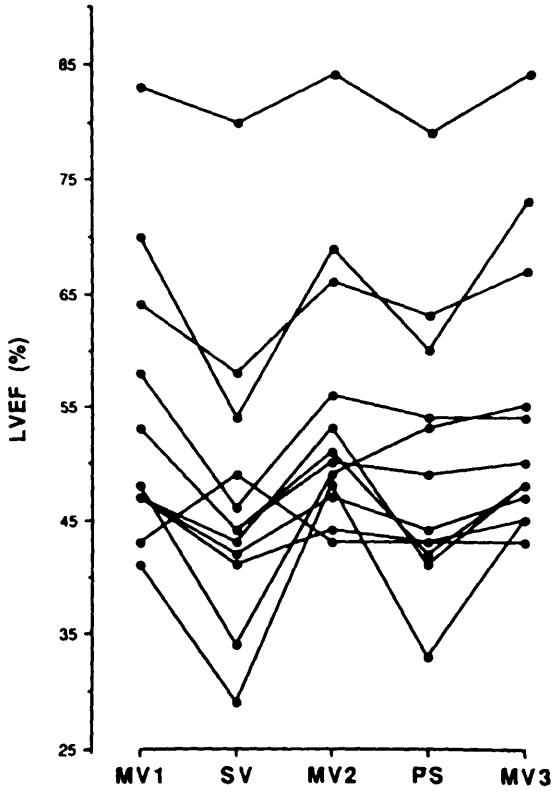


**Figure 5** Individual values of the evolution of left ventricular ejection fraction (LVEF) from mechanical ventilation ($MV_1$, $MV_2$, $MV_3$) to spontaneous ventilation (SV) and inspiratory pressure support (PS) in 12 patients with COPD but without left ventricular disease. (From Ref. 90.)

unlikely because no marked hypercarbia was observed and because 201 Thallium myocardial perfusion tomoscintigraphy did not reveal during weaning any perfusion defect, suggesting segmental myocardial ischemia (90).

The hypothesis of weaning-induced increased LV afterload suggested by the above study was specifically addressed in a subsequent study comparing the changes during weaning of LV end-systolic stress—an echocardiographic index of LV afterload—between a group of 12 patients without cardiopulmonary disease and a group of 11 patients with both COPD and LV disease (91): end-systolic stress was unchanged in the first group, while significantly increased during weaning of patients with cardiopulmonary disease (91) (Fig. 6).

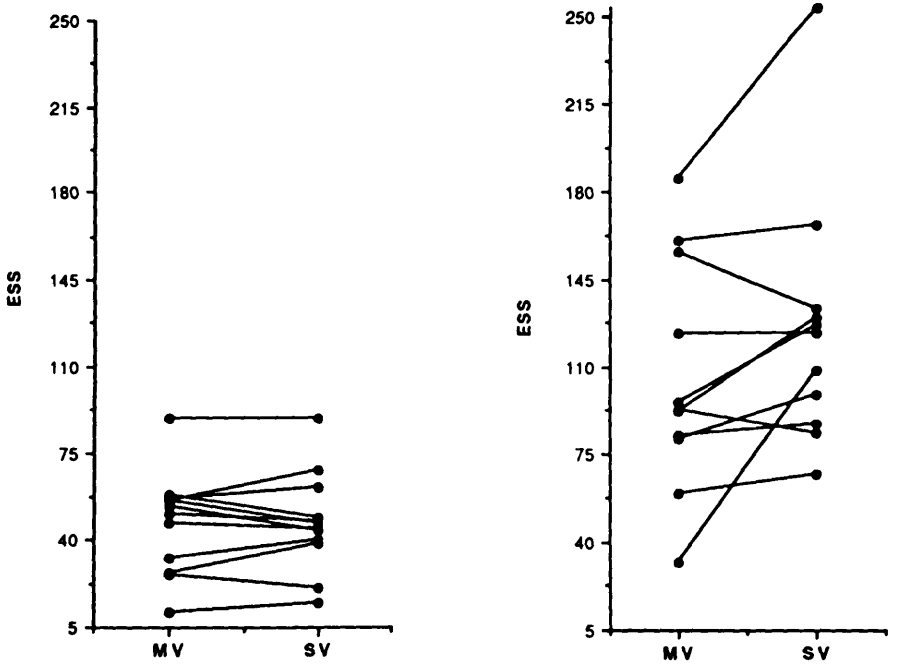


**Figure 6** Individual values of the evolution of end systolic stress (ESS)—an echocardiographic index of left ventricular afterload—from mechanical ventilation (MV) to spontaneous ventilation (SV) in a subgroup of 12 patients without cardiopulmonary disease (left panel) and in a subgroup of 11 patients with COPD and left ventricular disease (right panel).

### C. Summary

During weaning of patients with both COPD and LV disease, negativation of intrathoracic pressure combined with increased abdominal pressure and catecholamine release may potentially initiate a cascade of deleterious events and result in a vicious circle, which if unopposed leads to LV failure and CPE. Additionally, diaphragmatic fatigue may occur if the increased blood supply requirements of working respiratory muscles are not provided. CPE and diaphragmatic fatigue require the reinstitution of MV. It is of note that even in high-risk patients, such a vicious circle can be avoided so that the increase in PAOP will not occur and weaning will be easy (92).

We have reviewed some clinical studies in which direct or indirect arguments suggest the role of increased systemic venous return and/or ventricular interdependence and/or myocardial ischemia and/or increased LV afterload in the development of a CPE during weaning. In some of these studies, diuretics (83) or

vasodilators (89) were found to be beneficial in preventing CPE and easing weaning in small series of patients who failed to wean because of acute LV dysfunction. The potential benefits of some specific ventilatory procedures (CPAP, pressure support) need to be evaluated in weaning strategies for such patients.

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# 16

# Sleep in Acute Respiratory Failure of Chronic Obstructive Pulmonary Disease

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The importance of sleep breathing disturbances in acute respiratory failure of chronic obstructive pulmonary disease (COPD) is not yet well defined. A minority of COPD patient also have obstructive sleep apnea, which can be a major contributor to development of chronic and even acute respiratory failure. More subtle abnormalities may put patients in acute respiratory failure (ARF) at risk of developing unstable respiration or dangerous hypoxemia or hypercapnia when they fall asleep.

## I. Pathophysiology of Respiration During Sleep in COPD

Aspects of the pathophysiology of respiration in sleep in COPD have been reviewed recently (1–3). Research has focused on hypoxemia, hypoventilation, airways resistance, and changes in functional residual capacity (FRC).

### A. Hypoxemia

Many COPD patients have episodes of hypoxemia during rapid eye movement (REM) sleep, due to a combination of transient hypoventilation and $\dot{V}/Q$ distur-

bance, which may worsen because of a fall in FRC in sleep (1,3,4). The drops in $P_{O_2}$ are associated with rises in pulmonary artery pressure (5,6).

Not all patients with COPD have important episodes of nocturnal oxygen desaturation. Those who do tend to have worse disease judged by mechanics measurements (7). But desaturation is also worse in those who have daytime hypercapnia (8) and can be correlated with awake ventilatory response to $CO_2$ and to a lesser extent with reduction in ventilatory expense to hypoxia (9,10), which suggests either that chemoreceptor sensitivity helps prevent marked drops in saturation or that transient hypoventilation or desaturation in sleep tends to blunt chemoreceptor sensitivity. In general, as patients get worse, as judged by daytime blood gases and pulmonary function tests, they are more likely to have nocturnal oxygen desaturation (7). Patients who do have nocturnal oxygen desaturation, compared to others with equivalent daytime blood gases and mechanics, tend to have slightly higher pulmonary artery pressure at rest (11) and greater increases of pulmonary artery pressure at exercise (12). Survival in COPD patients without marked daytime hypoxemia but with frequent transient episodes of desaturation is not as good as for those without such episodes (13,14). On the other hand, using different criteria for oxygen desideration in a group of patients with more severe disease, the Edinburgh group found no prognostic significance of nocturnal desaturation beyond the information available from daytime blood gases (15,44).

### B. Hypoventilation

Normal subjects and COPD patients when asleep show a decrease in ventilation through stages NREM 1–4 and REM (16–21) with an average rise in arterial $P_{CO_2}$ of from 2.8 to 6.5 mmHg (22–28) and a corresponding decrease in inspiratory effort assessed as occlusion pressure (16). In hypercapnic COPD patients the rise in $P_{CO_2}$ in sleep (averaged from about 14 values taken through the night) was less than 2 mmHg (29). The maximum values of $P_{CO_2}$ recorded through the night in another study by intermittent sampling of arterial blood were higher than the maximum values seen in sleeping normal subjects; large rises were recorded in REM sleep in some patients (27). When oxygen was given, the 10 patients of Leitch et al. had a mean rise in $P_{CO_2}$ of 5.3 mmHg, but there were considerable differences between subjects. In one, who had a mean sleeping $P_{CO_2}$ of 62 mmHg on air, oxygen induced a rise in mean $P_{CO_2}$ to 71 mmHg, and marked variations were seen through the night in $P_{CO_2}$, between 63 mmHg in NREM and 83 mmHg in REM. Another study of six patients with daytime $P_{CO_2}$ ranging from 37 to 55 found the mean rise in sleep $P_{CO_2}$ between NREM and REM was only 3 mmHg (5) and similar results were found by Catterall et al. (20). The decrease in minute ventilation in sleep is likely due to a combination of increased airways resistance and decreased respiratory output (16).

### C. Functional Residual Capacity

Measurements of FRC in sleep in COPD are difficult and doubtful. One study using inductance plethysmography (18) found there were drops in FRC most marked in patients who desaturated in REM sleep, but another study using the more reliable body plethysmograph (16) found no change in FRC sleep.

### D. Airways Resistance

In five nonhypercapnic patients with COPD who did not have sleep apnea, upper airway resistance increased from 5.9 cm $H_2O$/L/sec in wakefulness to 9.6 in light NREM, 11.2 in deep NREM, and 15.6 in REM sleep (16). Lower airway resistance increased progressively through the night but did not depend on sleep state. Several authors have found that some, but not all, COPD patients show a tendency for nocturnal worsening of forced expiratory flow rates (30–32).

## II. Overlap of COPD and Obstructive Sleep Apnea

With the discovery of obstructive sleep apnea (OSA) it was postulated that some combination of OSA and COPD might be responsible for development of the blue and bloated syndrome of COPD associated with obesity, cor pulmonale, and daytime hypercapnia (3).

Among patients referred to sleep clinics and found to have obstructive sleep apnea, a certain percentage also have COPD, and these are more likely to have daytime hypoxemia, hypercapnia, and elevated pulmonary artery pressure than the patients with sleep apnea alone. In a recent series, 10% of patients diagnosed with sleep apnea had COPD (defined as FEV/VC $< 0.6$), and of these, one-quarter had respiratory failure (daytime $CO_2 > 45$ mmHg) compared to 8% of sleep apnea patients without COPD. In other series, those sleep apnea patients who developed hypercapnia (33) or cor pulmonale (34) also had airways obstruction. Other studies have found that sleep apnea patients who develop pulmonary hypertension are much more likely to have COPD then those who do not (2,35,47).

The other side of the coin is the potential for sleep apnea or nocturnal high upper airway resistance to favor the development of chronic respiratory failure in COPD patients. One recent study comparing hypercapnic with normocapnic COPD patients (none of whom had sleep apnea) found that daytime hypercapnia was associated with snoring, small upper airway size, and heavy alcohol consumption, suggesting that high upper airway resistance during sleep might indeed be a factor (36). Among patients with clinical COPD who also had sleep apnea with daytime hypersomnolence, Guillemenault et al. (37) found a high rate of daytime hypercapnia and hypoxemia, even though the degree of airways obstruction was relatively mild in some of the cases.

These observations indicate that the combination of obstructive sleep apnea and COPD is a bad one, carrying with it a substantial risk of pulmonary hypertension, $CO_2$ pulmonale, and hypercapnic respiratory failure. For the COPD patient the extra mechanical load of high upper airways resistance at night, even without sleep apnea, likely causes hypoventilation and contributes to the gradual development of respiratory failure.

## III. Sleep Loss and Control of Breathing

COPD patients acutely ill with conditions that threaten to precipitate acute respiratory failure can be assumed to sleep worse than when they are well. Sleep deprivation and sleep fragmentation may have adverse effects on ventilatory control. COPD patients not in acute failure have sleep fragmentation and reduced slow wave sleep and REM sleep (38). Sleep fragmentation has no effect on ventilatory response to $CO_2$ in normal subjects (39), but short-term sleep loss does reduce the slope of the ventilatory response curve (40). A small study of patients with COPD after one night of sleep deprivation showed no significant change in resting blood gases or ventilatory response to $P_{CO_2}$ (41). It is an open question whether more severe sleep deprivation could have an adverse effect during episodes of ARF.

## IV. Clinical Scenarios in ARF of COPD

### A. Severe Respiratory Failure Due Mainly to OSA

Some patients with OSA are first identified when they are brought to an intensive care unit with an episode of acute respiratory failure precipitated by a presumed infection, heart failure, or embolism (46). These patients are usually obese and have a long-standing history suggesting sleep apnea, but the history may not be available at the time. Because many of them smoke and have some reduction in $FEV_1/VC$ ratio, even though this is mild and not a major contributor to their respiratory failure, a diagnostic label of pure COPD with ARF may be erroneously applied. Intubation and mechanical ventilation aimed at COPD can accidentally provide adequate initial management for OSA. It is essential, however, that the diagnosis of COPD by verified, and that the OSA be considered, identified, and treated in the post-ICU hospital stay.

### B. Transient Upper Airway Resistance Problems

In patients with pharyngeal abnormalities (small cross-sectional area, high compliance) that predispose them to OSA, relatively small changes in the passive mechanical properties of the pharynx may precipitate OSA. It is not uncommon to see clinical features of upper airway obstruction in sleep in patients with edema from cor pulmonale or heart failure and then have the problem resolve after

diuresis, presumably because edema of the pharyngeal mucosa had caused temporary narrowing or collapsibility of the airway.

### C. ARF Against a Background of More Severe COPD plus OSA

Some patients with COPD also have a substantial degree of OSA. When they develop ARF, both the COPD and the sleep apnea can be assumed to be important factors. Initial treatment with intubation, ventilation, or CPAP is often adequate for both conditions. The problem is to recognize the sleep apnea component and make sure it is treated after extubation or withdrawal of CPAP or nasal ventilation. Some authors have emphasized that COPD patients with sleep apnea are markedly somnolent and have a history of snoring, but the diagnosis may not be so obvious. Experience with uncomplicated OSA patients indicates that some of them are resistant to the effects of sleep fragmentation and may complain very little of somnolence in spite of frequent nocturnal apneas, desaturations, and arousals. In addition, patients with chronic respiratory failure due to OSA often have a marked diminution of intensity of their snoring, perhaps because of diminished sensitivity to hypoxia with smaller negative inspiratory pressures, so there is not enough energy dissipated across the upper airway to excite snoring, or perhaps from changes in mechanics of the upper airway itself. In addition, relatively mild increases in inspiratory resistive load that would be sustainable without any problems by otherwise normal subjects may nevertheless make an important contribution to decompensation of a system already loaded by the mechanical and control problems of COPD. Physicians should therefore have a low threshold for suspicion of OSA in the background of patients with COPD in ARF.

Even if the diagnosis is suspected, there are considerable difficulties in proving it. Many OSA patients when they reach the stage of respiratory failure tend to show less cyclical breathing with obvious apneas and a greater tendency to have just high upper airways resistance in sleep with marked hypoventilation, worse in REM sleep. In COPD patients in respiratory failure, the devices used to detect apneas and hypopneas lose their reliability. The reliability of oxygen saturation to detect hypoventilation or apnea is reduced when enough supplemental oxygen is given to raise saturation to near 100%. Detection of obstructed efforts through paradoxical movements seen with impedance plethysmography is not likely to be reliable in COPD patients in ARF, who often have abnormal chest wall movements in any case. Even with esophageal pressure measurements, it can be difficult to detect changes in upper airway resistance against the background of high lower airway resistance. If the upper airway does get obstructed, the ensuing pleural pressure swings may not be much greater than during breaths with an open upper airway. In addition, because of reduced responsiveness to hypoxia or hypercapnia, the patient in ARF may not show the progressive increase in respiratory effort that is expected at the end of an obstructive or mixed apnea.

Mechanics assessment can be refined by measuring flow rate with a mask and a pneumotachograph, but in the COPD patient in ARF, it is necessary to be concerned about the addition of even a small dead space, which could have a major impact on alveolar ventilation in these patients. The best assessment may turn out to be direct measurement of pressure drop across the upper airway, but this requires special instrumentation with pharyngeal pressure sensors, which may not be easily tolerated and are difficult to position accurately, together with a mask to measure flow in order to assess resistance. Given all these problems, one may be tempted to administer nasal CPAP, the treatment for OSA, as a therapeutic experiment. But this approach has its own difficulties. Many ICU patients will not tolerate nasal CPAP, and there is always the possibility of an important dead space problem. All of the problems in assessing whether there is significant upper airway obstruction in the first place also apply to the process of determining whether the level of CPAP is adequate. And CPAP is not a specific treatment for OSA; it can provide a substantial benefit to patients with severe COPD. The ideal CPAP pressure prescription might need to take into account an assessment of intrinsic PEEP as well as upper airway mechanics.

Finally, application of nasal CPAP to OSA patients in respiratory failure is potentially hazardous. In the sleep laboratory, when patients with $CO_2$ retention are placed on CPAP for the first time, many show prolonged episodes of REM sleep during which they can have severe central hypopneas or apneas and hypoventilation, with a risk of severe respiratory acidosis and hypoxemia. Some kind of intermittent positive pressure device may then be required to maintain reasonable alveolar ventilation in sleep.

Because of the limited experience, the many unknowns, and the potential hazards, assessment and treatment of sleep disturbed breathing in COPD patients in the ICU should be approached with care and sophistication. Monitoring of arterial $P_{CO_2}$, not a usual feature of sleep apnea diagnosis, is strongly recommended, whether by frequent arterial blood sampling or by a transcutaneous probe carefully validated in the individual patient. This area is an interesting challenge for clinical investigators. In the meantime, a practical, safe approach when patients with ARF of COPD are suspected of having OSA is intubation, with or without ventilation. If OSA is an issue, of course, the criteria for extubation are different from the usual ones. Once the patient is stable, no longer in ARF, and extubated, a more routine and reliable assessment of any sleep breathing disorder can be performed in a sleep laboratory or with portable monitoring.

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# 17

## The Perioperative Period as a High-Risk Situation

### Management of Surgery and Anesthesia in Patients with Chronic Obstructive Pulmonary Disease

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## I. Introduction

Despite major advances in anesthetic and surgical techniques, the perioperative period remains a time of high risk for patients with chronic obstructive pulmonary disease (COPD) and limited respiratory reserves. Complications, such as hypoventilation, atelectasis, retained secretions, aspiration, pleural effusion, pneumonia, and thromboembolism, may occur and lead to respiratory failure in these patients. Upper abdominal surgery (UAS) and thoracic surgery (TS) are known to be associated with a higher incidence of postoperative pulmonary complications (PPC) than lower abdominal or peripheral surgery. These postoperative respiratory complications are more frequent in patients with some predisposing factors. Important intra- and postoperative physiological changes are induced by the surgical procedure, the anesthetic technique, postoperative pain, and the postoperative therapeutic regimen. All of these may affect respiratory drive, respiratory muscle dysfunction, lung and chest wall restriction, and airways obstruction. This chapter will focus on these different factors and their implications for the perioperative management of COPD patients.

## II. Postoperative Morbidity and Mortality in COPD Patients

Different risk factors contribute to postoperative morbidity and mortality, namely, age, sex, weight, smoking habit, pulmonary status of the patient, the type and the duration of surgery, and anesthesia. The role of these different risk factors has been shown in a limited number of studies conducted during the last 30 years, during which time the improvement in the standard of care and the development of postoperative mechanical ventilation has induced a decrease in postoperative morbidity and mortality.

### A. Age

Advanced age has been clearly identified as a factor increasing the incidence of PPC. Wightman showed in 1968 that the incidence of PPC in patients subjected to abdominal surgery was 8.9% for those under the age of 70 years, while it reached 16.5% for those over the age of 70 years (1). In 1973 Tarhan et al. reported in a group of 357 men with moderate to severe COPD subjected to general anesthesia and surgery that overall postoperative mortality increased form 7.7% in the 50- to 59-yr group to 16.7% in the 70- to 79-yr group (2). In this study, 33 out of the 38 deaths were the consequence of respiratory failure.

More recently, Pedersen et al. reported that, in a population of 7306 patients undergoing anesthesia and surgery (excluding of thoracic and cardiac surgery) (1) the incidence of PPC increased significantly with age, from 2.3% in those <50 yr to 10.2% >80 yr and (2) in-hospital mortality increased significantly with age, from 0.6% in the 40- to 49-yr group to 2.2, 2.9, and 5.8% in the 60- to 69-, 70- to 79-, and >80-yr groups, respectively (3,4). However, in contrast to the previous study, cause of death could not be related to development of PPC.

Some types of surgery, such as thoracic or vascular surgery, are performed in groups of patients with a high prevalence of COPD. Ginsberg et al. showed in patients undergoing pulmonary resections for lung cancer that advanced age influenced mortality rates, which were 1.3% for those under 60 years, 4.1% in the 60- to 69-yr group, and 7.1% for those over 70 years. In this group of patients, the major cause of death was related to postoperative pulmonary complications and included postoperative pneumonia and respiratory failure (29% of postoperative mortality), bronchopleural fistula, empyema, and pulmonary embolism. In abdominal aortic reconstruction, age was shown to influence postoperative mortality, which increased from 1.0% in those less than 60 years of age to 8.1% in those older than 60 ($p < 0.001$) (5).

Therefore, it appears that advanced age can clearly be considered a major contributing factor for PPC and postoperative mortality. However, with the development of postoperative intensive care management, including wider use of

postoperative mechanical ventilation, the contribution of PPC to the increased postoperative mortality in elderly patients is more difficult to establish.

### B. Sex

Most studies have found a higher incidence of PPC in males than in females. Tarhan et al. reported that the mortality rates for men and women with COPD were 9.2 and 2%, respectively (2). In major elective surgery, Pedersen found that males developed PPC with a greater incidence than females: 17.2% vs. 7.8%. Moreover, mortality rates were also significantly higher in males than in females (4). However, this difference can probably be related to the different types of surgery performed, with a large number of minor gynecological procedures in women.

### C. Obesity

Obesity is frequently reported to influence the incidence of PPC. Latimer et al. reported that PPC developed in 95% of 19 obese patients undergoing upper abdominal surgery (6). Although obese patients have a 10-fold increase in the incidence of wound complications and develop more profound hypoxemia and alterations in postoperative pulmonary function, the increased influence of obesity on PPC has not yet been established. Combining 10 different studies of morbidly obese patients having gastric bypass with gastrojejunostomy, Pasulka et al. reported a global PPC rate of 3.9%, although the criteria used for this complication were not uniformly defined (7).

### D. Type of Surgery

The nature of the surgical procedure has always been found to be a major determinant of PPC and postoperative mortality. Upper abdominal and thoracic surgery are usually associated with a greater incidence of PPC than lower abdominal surgery and peripheral surgery.

Wightman showed that the incidence of PPC was 10.3% after abdominal surgery, while it was 0.6% after nonabdominal surgery (1). Tarhan et al. showed that in male patients with moderate or severe COPD, postoperative mortality rates were significantly greater after thoracic and upper abdominal surgery (12.7%) than after lower abdominal and peripheral surgery (6.3%) (2). More recently, Pedersen et al. demonstrated that the incidence of PPC was 1.8% after minor surgery, 10.6% after major surgery, and 33.2% when upper gastrointestinal operations only were considered (3). These differences are highly significant. When looking at in-hospital mortality, patients with COPD had a mortality rate of 0% after minor surgery and 4.5% after major elective surgery.

Thoracic surgery for lung cancer is still associated with a high mortality rate. In patients undergoing pneumonectomy for lung cancer, Wahi et al. reported

a perioperative mortality rate of 7% (8). In addition, the incidence of major PPC, such as major atelectasis, pneumonia, and retained secretions, was 6.6%, while the incidence of patients requiring prolonged postoperative mechanical ventilation (>48 hr) was 9.1%. In a multicenter study collecting 2200 patients subjected to pulmonary resections for lung cancer, Ginsberg et al. found 30-day mortality rates of 2.9% after lobectomy and 6.2% after pneumonectomy (9).

Abdominal aortic surgery is frequently performed in patients with COPD. In a group of 173 patients undergoing abdominal aortic reconstruction, 44% of whom having a COPD, Baron et al. observed a 56% incidence of PPC (10). However, postoperative mortality was not influenced by PPC, in contrast to postoperative cardiac complications. Diehl et al. in a study of 557 patients subjected to abdominal aortic surgery, found similar results with an incidence of postoperative respiratory failure requiring prolonged mechanical ventilation for 5.9% of patients (5). However, in contrast to postoperative myocardial infarction, respiratory insufficiency was a rare cause of postoperative mortality in these patients, responsible for only 0.2% of postoperative deaths.

### E. Duration of Anesthesia and Surgery

The duration of anesthesia and surgery has been frequently considered to be a major contributing factor in the development of PPC. Tarhan et al. reported that in men with COPD, postoperative deaths significantly increased with the duration of anesthesia and surgery, the mortality rate increasing from 5.3%, when the duration of general anesthesia was <120 minutes, to 12.1% when it was >120 minutes (2). Similar results were reported by Wightman, who found that the incidence of PPC after abdominal operations was 7.4% when the duration of surgery was 0–30 minutes increased to 11.9 and 12.8% when the duration of surgery was 31–60 and 61–120 minutes, respectively (1). More recently, Pedersen et al. reported that the incidence of PPC significantly increased from 0.6 to 13.4 and 30.2% when the duration of anesthesia increased from 0–30 to 180–299 and more than 300 minutes, respectively (3).

However, the duration of anesthesia is usually related to the type and the technical difficulty of the surgical procedure. The more difficult the nature of surgery, the longer the duration of anesthesia. When upper abdominal and transvesical operations were analyzed separately from the other abdominal cases, Wightman found that the incidence of PPC in these groups was independent of the duration of surgery (1). Therefore, it can be misleading to consider the duration of anesthesia as a risk factor independent from the nature of surgery.

### F. Smoking History

Smoking has been shown to influence the incidence of PPC, which is higher among smokers than among nonsmokers. Latimer et al. found in a small group of

patients subjected to upper abdominal surgery that 35% of patients who developed macroatelectasis were smokers, while none of the patients without atelectasis smoked (6). More recently, Warner et al. confirmed this finding in a retrospective study including 500 patients undergoing coronary artery bypass grafting surgery (CABG). PPC rates were 11.4% in the nonsmokers and 40% when the degree of smoking was greater than 20 pack-years (11).

### G. COPD

The link between COPD and the development of PPC has been established in upper abdominal and thoracic surgery. Considering all types of surgery, Tarhan et al., in a retrospective study performed in 1967–1970, demonstrated that mortality rates were 2.2% in non-COPD patients and 10.6% in COPD patients, among whom deaths were mostly due to respiratory failure (2). More recently, Jayr et al., in a prospective study of 146 patients undergoing abdominal cancer surgery, found that PPC were observed in 60% of COPD patients and in 19% of non-COPD patients (12). Pedersen et al. demonstrated that the incidence of PPC, which was 6% following all types of operations in the overall population, was increased to 17.9% in COPD patients after major surgery and reached 32% in emergency surgery (3). In contrast, with minor surgery the incidence of PPC in COPD patients was 4.7%, not statistically different than in the other patients. In-hospital mortality rates were also increased by the existence of COPD. After major surgery, mortality rate increased from 1.2% in the overall population to 4.5% in COPD patients. This was more pronounced after emergency major surgery.

### H. Type of Anesthesia

Type of anesthesia has never been shown to markedly influence postoperative morbidity and mortality. Different retrospective studies have shown that postoperative mortality is greater in patients undergoing surgery under general anesthesia than under loco-regional anesthesia (2). However, in these studies the choice of anesthetic technique, as well as the indication and contraindication of the surgical procedure, may have been influenced by the nature of the operation and the severity of the pulmonary disease.

Yeager et al. prospectively compared either general anesthesia or the combination of epidural anesthesia with light general anesthesia on the postoperative course of patients undergoing abdominal and thoracic surgery (13). These authors found that mortality was greater in patients with general anesthesia. Other studies also found a lower incidence of atelectasis in patients undergoing cholecystectomy under epidural anesthesia than under general anesthesia alone or the combination of epidural and general anesthesia (14). However, these results were not confirmed in other studies. Baron et al. prospectively studied patients undergoing abdominal aortic reconstruction under either general anesthesia or the combina-

tion of thoracic epidural anesthesia with light general anesthesia and found no difference in postoperative mortality or morbidity in the two groups of patients (10).

## III. Respiratory Consequences of Surgery

Different alterations in respiratory function occur during the postoperative period. These respiratory impairments, essentially observed after upper abdominal and thoracic surgery and to a lesser degree after lower abdominal surgery, may play a role in the genesis of postoperative respiratory complications. Some of them are already present when the patients emerge from anesthesia; some are not present during the recovery period and appear progressively during the first postoperative day.

### A. Respiratory Changes After Upper Abdominal Surgery

Such changes include a restrictive syndrome, hypoxemia, change in the pattern of breathing, increased work of breathing, and respiratory muscle dysfunction.

In comparison to preoperative values, vital capacity and $FEV_1$ decrease by approximately 60% after upper abdominal surgery and by 40% after lower abdominal surgery (15). This restrictive syndrome is immediately maximal, present as soon as the patients emerge from anesthesia, then progressively recovers over 1–3 weeks (16).

Functional residual capacity (FRC) decreases by 30% during the postoperative course. This decrease is maximal at the end of the first postoperative day. In the absence of further complications, FRC returns progressively to its preoperative level within 1–2 weeks. Since general anesthesia is also responsible for a decrease in FRC, the separation between the intra- and postoperative decrease in FRC has been questioned. However, Ali et al. have shown that FRC returns almost to its preoperative value during the first few postoperative hours, then decreases progressively, to be significantly decreased 16 hours after the end of surgery (16). This delayed decrease in FRC suggests that the mechanisms responsible for the anesthesia-induced and surgery-induced decreases in FRC are different.

Hypoxemia is another typical feature of the postoperative period of upper abdominal surgery (15). Decreases in $Pa_{O_2}$ usually strictly follow changes in FRC.

The pattern of breathing also changes during the postoperative period (17). Minute ventilation usually remains unaltered after surgery, while patients breathe with a smaller tidal volume and a higher respiratory rate than preoperatively. Postoperative pain has frequently been suggested to induce this rapid and shallow breathing. Actually, it has been shown that this breathing pattern persists after profound pain relief using opiate analgesia, suggesting that other mechanisms may be involved in this breathing mode (17).

The work of breathing has been shown to be increased in the postoperative period of upper abdominal and thoracic surgery. In patients undergoing upper abdominal surgery, Neely et al. showed that the respiratory work was always markedly increased during the first postoperative days (18). In thoracic surgery for lung cancer, Maeda et al. also demonstrated that the work of breathing increased from 0.45 ± 0.04 kg.m/min before surgery to 0.87 ± 0.11 kg.m/min during the early postoperative period (19). Furthermore, the patients who required prolonged postoperative mechanical ventilation had the greatest increase in postoperative work of breathing. These changes are probably associated with an increase in the drive to breathe that has been observed postoperatively, as shown by the postoperative increase in the occlusion pressure (17).

### B. Respiratory Changes After Thoracic and Cardiac Surgery

Pulmonary complications are frequent after thoracic and cardiac surgery. In patients undergoing thoracic surgery for lung cancer, the operative mortality rate ranges from 2.1 to 12.4%, the first factor involved in this mortality being pulmonary complications. In cardiac surgery, the incidence of pulmonary complications is much lower than in thoracic surgery. Postoperative pneumonias are observed in 0.6% of patients undergoing coronary bypass surgery (20). However, pulmonary complications still are the second most important factor in increased length of hospital stay, after wound infection.

The respiratory changes that occur after thoracic surgery are similar to those described after upper abdominal surgery, although they are somewhat less severe. Vital capacity and $FEV_1$ decrease by 40–50%. Functional residual capacity decreases by 20–30%, and hypoxemia is also observed during the first postoperative days when the patients do not receive supplemental $O_2$. As for upper abdominal surgery, the same factors have been speculated to explain these respiratory changes.

In cardiac surgery, left lower lobe atelectasis is reported to be present in 86–90% of patients during the immediate postoperative period. While the factors involved in the respiratory complications of upper abdominal surgery may also be responsible for the respiratory changes observed after thoracic and cardiac surgery, cardiac surgery may be associated with specific complications related either to extracorporeal circulation or to cardiac cooling.

### C. Phrenic Nerve Injury After Cardiac Surgery

The left phrenic nerve, which is positioned between the pericardium and the left pleura, is exposed to intraoperative hypothermic injury during the period of cold cardioplegia during cardiopulmonary bypass surgery. In dogs, Dureuil et al. demonstrated that a topical cooling of the phrenic nerve could induce a complete block of phrenic nerve conduction and emphasized the importance of the duration

of the topical cooling (21). While a rapid recovery was demonstrated after 5-minute cooling, 30-minute cooling was associated with a prolonged impairment of phrenic nerve conduction.

In a nonrandomized study in humans, Benjamin et al. showed the possible influence of ice cooling of the heart on the development of postoperative atelectasis (22). Left lower lobe infiltrates were present in 65% of patients when topical cooling of the heart was used and in 30% of patients in the absence of cooling. The excursion of the left hemidiaphragm was shown to be decreased in 69% of patients with left lower lobe infiltrates, suggesting the possible influence of impaired diaphragmatic function on the development of atelectasis.

Estenne et al. studied 12 patients before and 8–13 days after CABG (23). After surgery, vital capacity was decreased by 20% and FRC by 9.5%. The conduction times of the right and left phrenic nerves and the ratio of the EMG activity of left and right hemidiaphragms were unchanged after surgery in 11 of the 12 patients. These authors concluded that phrenic-diaphragm dysfunction is rarely involved in the postoperative loss of lung volume. However, this study was performed during the second postoperative week, when most of the postoperative alterations in respiratory function have recovered.

In order to establish the relationship between intraoperative cold cardioplegia and phrenic nerve injury, Wilcox et al. measured the phrenic conduction time during phrenic nerve stimulation in 57 patients before and after cardiac surgery (24). They found a postoperative abnormality in phrenic nerve function in 5 patients, while left lower lobe atelectasis were present in 50 of 57 patients. These authors concluded that transient phrenic nerve injury was unlikely to be the explanation for the almost routine development of left lower lobe atelectasis. The intraoperative factors they found to be more frequently associated with postoperative atelectasis were intraoperative opening of the pleural space, duration of surgery, number of grafts, low body temperature, and lack of use of a polystyrene pad to protect the phrenic nerve from intrapericardial ice.

### D. Postoperative Dysfunction of Respiratory Muscles

Several studies have recently pointed out the possible responsibility of a diaphragmatic dysfunction for the postoperative respiratory changes observed after upper abdominal and thoracic surgery.

#### *Description of Postoperative Diaphragmatic Dysfunction*

A decrease in diaphragmatic activity was first posited to be responsible for postoperative respiratory dysfunction by Pasteur in 1914 (25). However, it is only recently that several studies tried to demonstrate the responsibility of diaphragmatic dysfunction in postoperative respiratory changes. In 1973, Tahir et al. observed, using fluoroscopy after abdominal surgery, a reduction in the excursion

of the diaphragm during tidal breathing (26). In 1983, Ford et al. studied the consequences of cholecystectomy on diaphragmatic function (Fig. 1) (27). The technique used by these authors to assess the relative contribution of the diaphragm during tidal breathing analyzed the changes in transdiaphragmatic pressure swings (Pdi) and in the ratio of gastric pressure over esophageal or transdiaphragmatic pressures (Pgas/Pes or Pgas/Pdi). Diaphragmatic function was also assessed by analyzing changes in the external abdominal dimensions, since an increase in the diameter or in the circumference of the abdomen during inspiration is usually associated with diaphragmatic contraction. They concluded that diaphragmatic function was decreased after surgery: the pattern of breathing, which was predominantly abdominal preoperatively, was shifted to predominantly thoracic after surgery. These changes were observed during the immediate postoperative period as well as 2 and 4 hours after the end of surgery, and values returned to preoperative levels 24 hours after surgery.

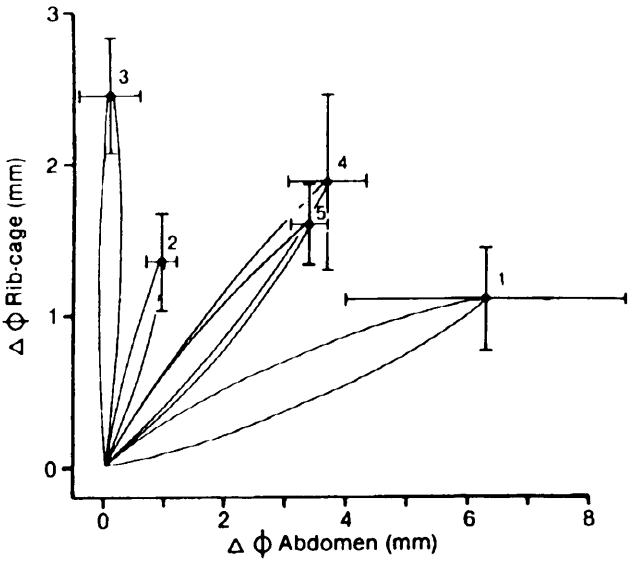


**Figure 1** Konno-Mead diagram of chest wall configuration in patients undergoing cholecystectomy. Change in rib cage diameter ($\Delta\phi$RC) was plotted against change in abdominal diameter ($\Delta\phi$Abbd) for each of the designated time periods. Each loop represented a tidal breath. These data showed a shift from predominantly abdominal breathing to a predominantly rib cage breathing. Bars indicate ± SEM. 1 = Control; 2 2= 2–4 hr postoperative; 3 = 6–8 hr postoperative; 4 = 24 hr postoperative; 5 = 48 hr postoperative. (From Ref. 27.)

In another study, Simonneau et al. reported the postoperative changes in diaphragmatic function in five patients after an elective upper abdominal surgery (28). Diaphragmatic function was assessed in this study by three different methods: changes in transdiaphragmatic pressure swings, changes in the circumferences of thorax and abdomen, and displacement of the diaphragm over the range of vital capacity using an ultrasound technique. All of these indirect indices of diaphragmatic function were markedly decreased on the first postoperative day. In some patients, a paradoxical inward motion of the abdomen was shown during inspiration. All alterations returned progressively to normal during the 7 postoperative days. It was also noted that good pain relief, achieved by an epidural administration of 150 μg of fentanyl, had no beneficial effect on diaphragmatic function.

The existence of postoperative diaphragm dysfunction induced by upper abdominal surgery has been challenged. Estimates of diaphragm contribution to inspiration were based on the relation between swings in gastric and pleural pressure and between swings in abdominal and rib cage expansion. However, these indices are not specific of diaphragm contribution to breathing (29). Decreases in the ratio of Pgas/Pdi or Pgas/Pes can be misleading if gastric pressure swings are induced by abdominal muscle contraction rather than by changes in diaphragm contraction. Furthermore, the drive to breathe increases during the postoperative period, as suggested by the postoperative increase in occlusion pressure (17), the increase in work of breathing (19), and the fact that ventilation remains unchanged in spite of an increase in lung impedance. With increasing drive to breathe, intercostal muscle activity increases proportionately more than diaphragm activity. This tends to lower the ratio Pga/Pes. Furthermore, the shift in ratio of rib cage to abdominal expansion does not necessarily imply a decrease in diaphragm contribution to breathing, but could be partly due to increased intercostal inspiratory activity associated with increased overall drive to breathe. In addition, some postoperative patients show tonic activity of abdominal muscle in inspiration, which makes the abdominal wall less extensible and enhances the ability of the diaphragm to expand the rib cage.

However, other arguments suggest that changes in these indirect indices of diaphragm function may still reflect the existence of postoperative diaphragm dysfunction. In dogs, the EMG activity of the diaphragm has been shown to progressively increase during the first few postoperative days, the time course of these improvements corresponding to the increase in pulmonary function observed in humans (Fig. 2) (30). In addition, Pansard et al. inserted EMG electrodes intraoperatively in the diaphragm of patients undergoing abdominal aortic surgery and observed that the diaphragm EMG signal was poor on the first postoperative day (31). Its increase, induced by an epidural administration of local anesthetic, was associated with a return to the preoperative values of respiratory rates and tidal volumes (32) (Fig. 3).

In addition to the decrease in diaphragm activity, Duggan and Drummond

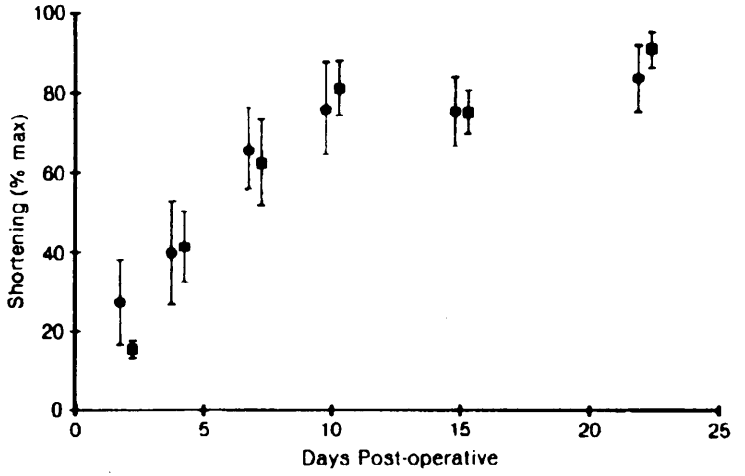


**Figure 2** Mean shortening during postoperative recovery. Closed circles: costal shortening; closed squares: crural shortening. Bars ± SD. Results are expressed as % maximum value recorded. (From Ref. 30.)

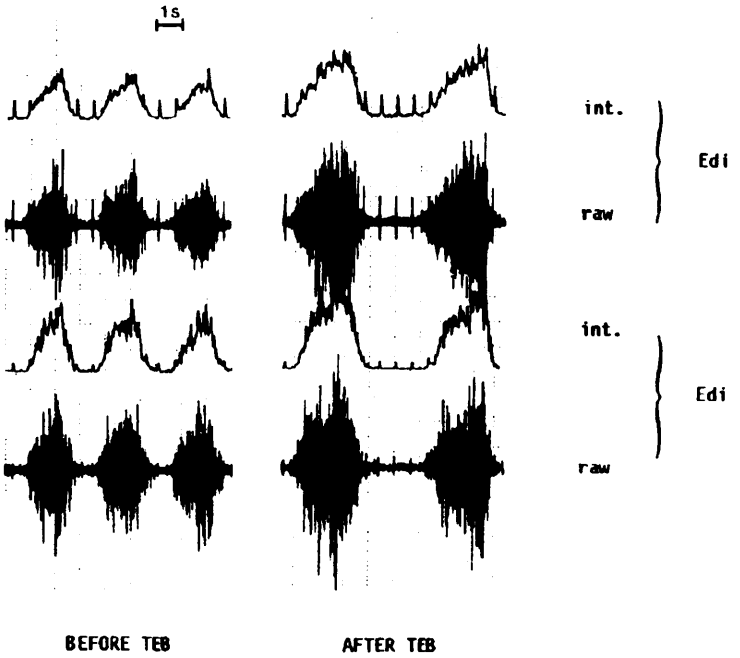


**Figure 3** Effects of thoracic extradural block (TEB) and raw (raw) and integrated (int) electromyogram of costal (Edi cost) and crural (Edi cru) parts of the diaphragm after upper abdominal surgery, before and after TEB. (From Ref. 31.)

also pointed out the changes in the activity of abdominal muscles induced by upper abdominal surgery (33,34). These muscles are progressively activated during expiration and abruptly relax at the onset of the following inspiration. This pattern of breathing could be falsely interpreted as an abdominal paradoxical breathing cycle. Abdominal muscles behave as inspiratory muscles after upper abdominal surgery in some patients, their relaxation contributing to the tidal volume. In dogs, Farkas and de Troyer have shown that midline laparotomy induces an inhibition of the transversus abdominis and an activation of the abdominal external oblique and of the triangularis sterni (35).

After thoracic surgery for pulmonary resection, Maeda et al. recently studied the changes in diaphragmatic function during the postoperative period (19). During the first few postoperative days, they observed a decrease in the maximal strength of the diaphragm, $Pdi_{max}$, and in the ratio of gastric over transdiaphragmatic pressure swings (Pgas/Pdi). Of the 20 patients studied, the lowest indices of diaphragmatic function were observed in four patients who developed postoperative respiratory failure requiring prolonged mechanical ventilation. These data suggest that thoracic surgery is responsible for some postoperative diaphragmatic dysfunction. For cardiac surgery, during the first few postoperative days similar results were found, with a shift from abdominal breathing to a predominantly thoracic breathing, again suggesting diaphragm dysfunction (36).

### *Mechanisms of Postoperative Diaphragmatic Dysfunction*

Different mechanisms have been thought to explain postoperative diaphragmatic dysfunction. A lingering effect of anesthesia might have been involved in the genesis of the diaphragmatic impairment. However, in an experimental study, Road et al. demonstrated that, when dogs were only anesthetized, no change in diaphragmatic function was observed, although diaphragmatic impairment was observed when a cholecystectomy followed anesthesia. No change in diaphragmatic function was observed after lower abdominal surgery (37).

A direct effect of the surgical trauma on the diaphragm was also ruled out by Dureuil et al. (38). In five patients undergoing upper abdominal surgery, diaphragmatic contractility was assessed by changes in the ratio of gastric pressure swings over transdiaphragmatic pressure swings (Pgas/Pdi), while both phrenic nerves were electrically stimulated on the neck. Four hours after surgery, no change in diaphragmatic contractility was noted. This suggested that postoperative diaphragmatic dysfunction was not the consequence of a decrease in diaphragm contractility, but rather resulted from a reflex inhibition of phrenic nerve output induced by the surgical trauma.

Previous reports have already described similar respiratory reflexes, such as an inhibition or a stimulation of respiration induced by a mechanical stimulation of either abdominal viscera or intercostal and abdominal muscle proprioceptor

afferents. Some of these afferents are conducted by medullary pathways, while others travel through the vagus or the phrenic nerves. Ford et al. showed in spontaneously breathing dogs that mechanical stimulation of the gallbladder was associated with an immediate fall of tidal volume and phrenic nerve output (39). The short interval between the gallbladder stimulation and the decrease in diaphragmatic contraction suggested that the mechanism involved was a neural reflex. Since similar results were obtained after vagotomy, most of the afferents of this inhibitory reflex were not traveling by the vagus nerve.

In favor of this hypothesis, Mankikian et al. showed in humans that a thoracic epidural block with local anesthetics (bupivacaine 0.5%), performed on the first day following upper abdominal surgery, could restore diaphragmatic function, assessed either by changes in gastric and esophageal pressure or by an increase in diaphragmatic EMG activity through EMG electrodes inserted intraoperatively (31,32) (Fig. 4). The epidural block also induced a decrease in postoperative respiratory rate and an increase in tidal volume, which returned to the preoperative values. Thoracic epidural blockade may be associated with different respiratory changes. It may interrupt both the afferent inputs originating from the abdominal viscera and from abdominal and chest wall and the efferent outputs reaching the abdominal and intercostal muscles.

The improvement in diaphragmatic function induced by the epidural block could be a consequence of the blockade of the afferent pathway interrupting an inhibitory reflex. However, the different indices used to assess diaphragmatic function are all influenced by variations in abdominal muscle activity. Both gastric pressure and abdominal dimensions are not specific to diaphragmatic activity. They are markedly influenced by contraction of abdominal muscles, which increase gastric and transdiaphragmatic pressures and decrease abdominal dimensions. Mankikian et al. pointed out the difficulty of analyzing diaphragmatic function indices, i.e., gastric pressure swings and abdominal dimension changes during the postoperative period in the presence of active contractions of abdominal muscles (32).

Therefore, it could be speculated that the motor block of 0.5% epidural bupivacaine, by cutting off the activity of abdominal muscles, just eliminated the interference due to the abdominal muscles contraction on the indices of diaphragmatic activity, rather than changed the real activity of the diaphragm.

## IV. Management of Anesthesia

Patients with UAS, TS, and CABG are at high risk for PPC with underlying chronic pulmonary disease. The clinical complications usually include retained secretions, atelectasis, and bronchospasm. These complications increase the work of breathing and may precipitate respiratory failure.

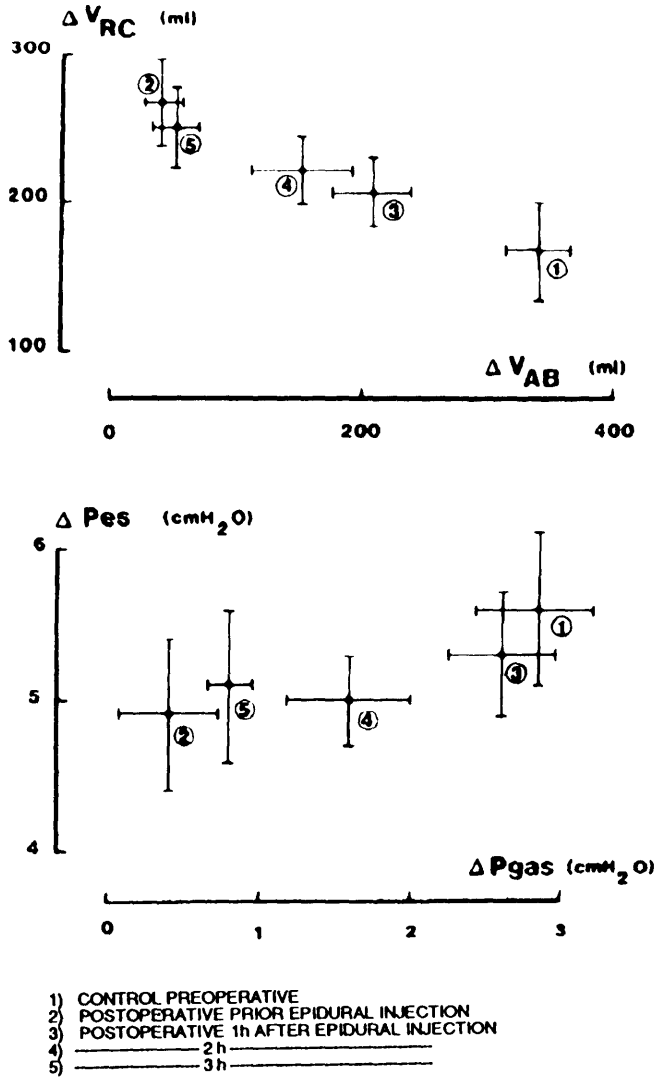


**Figure 4** Mean tidal changes in rib cage volume ($\Delta V_{RC}$) plotted against mean tidal changes in abdominal volume ($\Delta V_{AB}$) (upper panel) and mean inspiratory swings in esophageal pressure (ΔPes) plotted against mean inspiratory swings in gastric pressure (ΔPgas) (lower panel) for each of the designated time period. (From Ref. 32.)

The goal of anesthetic and surgical management is to minimize the consequences of anesthesia and surgery. This can be achieved by adequate care of the patients during the pre-, intra-, and postoperative periods.

### A. Principles of Anesthesia in COPD Patients

#### *Preoperative Period*

During the preoperative period, prevention of PPC can be achieved by three different methods: smoking cessation, optimization of respiratory condition, and preoperative practice of the techniques of physiotherapy that will be used postoperatively. Since it has been shown that smoking increases the risk of PPC, cessation of smoking should be recommended. The delay between smoking cessation and surgery has been shown to influence the incidence of PPC. In CABG surgery patients, Warner et al. observed no significant improvement in the incidence of PPC in patients who abstained from smoking for less than 8 weeks, in comparison to those who never stopped (56.4% vs. 48.4%) (11). In contrast, PPC rates decreased to an incidence of 15–20% when patients had stopped smoking for periods longer than 8 weeks prior to surgery.

#### *Anesthesia*

Once surgery has been decided upon, the choice between loco-regional techniques and general anesthesia must be made if the location of the surgical procedure allows both techniques.

##### General Anesthesia

The main effects of general anesthesia on the respiratory system are (1) respiratory depression, (2) bronchial hyperreactivity, and (3) alterations in gas exchanges. All anesthetic agents are potent ventilatory depressants. Intravenous anesthetic agents can be associated with apnea during the period following administration. With the exception of droperidol (40), they depress the ventilatory response to both carbon dioxide and hypoxemia. COPD patients are usually more sensitive to the respiratory depressant effect of these agents. Gross et al. have shown that, following the same dose of thiopental or midazolam, the decrease in the ventilatory response to $CO_2$ is more pronounced in COPD patients than in normal patients (41).

In order to prevent profound ventilatory depression, especially in COPD patients with $CO_2$ retention, it may be recommended that premedication be administered only when patients can be closely monitored, which is usually better achieved close to the operating room rather than in the ward. Moreover, when spontaneous ventilation is desired during general anesthesia, COPD patients will maintain spontaneous ventilation with higher values of $Paco_2$ (42). The intensity of the respiratory depressant effect of anesthetic agents may play an important role in COPD patients during the recovery period.

The second consequence of general anesthesia is the bronchial reactivity induced by anesthetic techniques and agents. COPD patients frequently have some bronchial hyperreactivity. Physical stimulation of the tracheal mucosa induced by the tracheal tube and mechanical ventilation with a cold and dry gas may therefore induce bronchoconstriction. Anesthetic agents may interfere with the reactivity of bronchial smooth muscle. In a recent preliminary study performed in asthmatic patients, Brown et al. showed that 29% of asthmatic patients developed wheezing during induction of anesthesia (43). In a canine model of asthma, Hirshman tested the effect of the different anesthetic agents on the prevention or the treatment of bronchospasm induced by the administration of an allergen or metacholine. They showed that thiopental has no specific effect on the development of bronchospasm. In contrast, inhalation agents, ketamine, or lidocaine decrease bronchial reactivity (44–46). Therefore, these agents will be used preferentially in patients with hyperreactive bronchi.

The third consequence of general anesthesia is alterations in gas exchange. General anesthesia induces a decrease in functional residual capacity and is associated with the development of atelectasis and alterations in gas exchange. In non-COPD patients, these gas exchange abnormalities consist mainly of a shunt. Abdominal and thoracic surgery can further extend these changes and increase the number of poorly ventilated areas of the lung. In COPD patients, the effect of general anesthesia on gas exchange is debated. Dueck et al. showed that anesthesia induces an increase in both shunting and perfusion of poorly ventilated lung units (47). These changes were greater in symptomatic pulmonary disease patients. The greater the preoperative gas exchange abnormalities, the more pronounced were the anesthesia-induced alterations in gas exchange. In contrast, Gunnarson et al. did not confirm these findings and showed in COPD patients that alterations consisted mainly of an increased mismatch between ventilation and perfusion of pulmonary areas without creation of a pulmonary shunt, in contrast to what is usually observed in non-COPD patients (48). These changes were observed after 15 minutes of anesthesia and did not increase further after another 30 minutes of anesthesia. CT scans performed before and after induction of anesthesia suggested that FRC did not decrease after induction of anesthesia in COPD patients. Cross-sectional thoracic area, which is 5–10% larger in COPD patients than in normal patients, remained unchanged after induction of anesthesia, with no development of atelectasis. This can be related to the decrease in the elastic recoil of the lung or to the altered chest wall mechanics of COPD patients. This was further documented by the cranial shift of the dome of the diaphragm, which was not displaced in 8 of 10 COPD patients, while it was shifted cranially in only 2 of 10 COPD patients.

Another consequence of anesthesia in COPD patients concerns the deleterious consequences of nitrous oxide, which may increase the volume of gaseous cavities. To prevent any further distention of bullous cavities, nitrous oxide should be avoided in patients with bullous disease or emphysema with large bullae.

### Loco-regional Anesthesia

In contrast to general anesthesia, loco-regional anesthesia induces minimal respiratory effects, even in COPD patients (49). During epidural anesthesia, FRC and gas exchange remain unaltered, while the ventilatory response to $CO_2$ is mildly stimulated (50,51). However, if epidural and spinal anesthesia both induce minimal reduction of inspiratory capacity, both techniques markedly decrease expiratory capacity due to the motor effects on abdominal muscles (49). Therefore, coughing is impaired during anesthesia. This can lead to clinical complications in COPD patients with hyperproductive bronchorrhea during long-lasting surgical procedures. The risk of bronchoconstriction is minimal during loco-regional anesthesia alone, since tracheal intubation is not required and local anesthetics decrease bronchial hyperreactivity (45). Therefore, even in the absence of convincing data in favor of a lower risk of PPC, loco-regional techniques are frequently preferred by anesthetists when the site of surgery is compatible with the anesthetic technique and when the duration of coughing impairment seems acceptable, no matter the degree of respiratory disease.

## B. Administration of Anesthesia

### *Premedication*

Due to the more pronounced ventilatory depressant effect of anesthetic agents in COPD patients, the dose of the sedative agent administered for premedication should be adapted to the degree of pulmonary disease. In COPD patients with $CO_2$ retention, premedication should be administered only when they can be closely monitored. This is usually better achieved close to the operating room than in the ward.

### *Anesthesia*

When general anesthesia has been chosen, the type of ventilation and airway control must be determined. Different studies have shown that during halothane anesthesia under spontaneous ventilation, the increase in $Paco_2$ is greater in COPD patients than in normal patients and is inversely related to the patient's $FEV_1$ (42). Therefore, although spontaneous ventilation can still be proposed for short procedures in COPD patients, anesthesia is always associated with marked increases in $Paco_2$. For long procedures or when surgery is responsible for an increase in the work of breathing due to the patient's positioning or to the intraoperative impairment of the respiratory system, tracheal intubation and controlled ventilation are usually preferred.

### *Induction of Anesthesia*

The choice of the anesthetic agent does not influence intra- and postoperative morbidity or mortality. In order to prevent bronchospasm induced by the insertion of the tracheal tube, agents that depress airway hyperreactivity should be used.

During the preinduction period, Hirshman et al. recommend an intravenous administration of 1.5 mg/kg of lidocaine. Among the different anesthetic agents, thiopental has been shown in a dog experiment not to decrease the bronchospasm induced by different stimuli, while ketamine and inhalation agents markedly decrease airway resistance. The usual clinical practice is therefore either to start with an intravenous agent, such as thiopental, which does not protect against the development of airway hyperreactivity and, after it, to start inhalation agents prior to the insertion of the tracheal tube. Propofol was recently shown to protect against airway hyperreactivity induced by tracheal inhalation. In emergency cases, ketamine may be the agent of choice because of both its protective effects on airway hyperreactivity and its beneficial hemodynamic effects.

Because ventilation with a cold and dry gas has also been shown to be responsible for the development of bronchospasm, the gas mixture should be rewarmed and humidified, either by using low fresh gas flows in a rebreathing circuit or by using heat-moisture exchangers or heated humidifiers in an open anesthesia circuit.

In the absence of bronchospasm during the course of anesthesia, controlled ventilation can usually be achieved with low inspiratory pressures. Because of increased airway resistance, the choice of the ventilatory settings should be oriented to a low respiratory rate, giving a long expiratory time and a low value of intrinsic PEEP. When end-tidal $CO_2$ is monitored, the gradient $Paco_2$-$PETco_2$, which is usually close to a mean value of 5 mmHg during anesthesia in normal patients, is markedly increased in COPD patients because of the elevated alveolar dead space.

### *Recovery Period*

The most important phase of anesthesia for COPD patients is the recovery period, since it involves both an increase in the ventilatory demand and a loss of the capabilities of the respiratory system. During this period, rewarming induces a marked increase in $O_2$ consumption (52). Furthermore, the increased work of breathing is responsible for an increase in respiratory $O_2$ consumption. These increases in demand may occur while the ventilatory system has lost part of its capacities. A persistent ventilatory depression is present because of the incomplete elimination of anesthetic agents. In addition, after upper abdominal and thoracic surgery, the alterations in the mechanical properties of the chest wall, already present during the recovery phase, reduce the ventilatory capabilities of the patients (52). Bay and Nunn have shown that during the shivering period, some patients may develop hypoxemia (53).

COPD patients have an increased airway occlusion pressure suggestive of an increased drive to breathing (54). Anesthetic agents induce in these subjects a ventilatory depression which is more profound and prolonged than in normal patients (41,42). This effect may play an important role in the postoperative ventilatory depression observed in these patients.

In these patients with limited respiratory reserves, it is common practice to prolong mechanical ventilation during the first postoperative hours until the patients have eliminated most of the anesthetic agents and recover a normal temperature and respiratory drive to breathing. The goal of this practice is to prevent the simultaneous accumulation of the remaining respiratory depressant effects of anesthesia, the increased $O_2$ consumption of the rewarming period, and the already present alterations of the chest wall mechanics induced by surgery (52).

### C. Choice of Surgical Technique

New techniques of laparoscopic surgery have recently been shown to reduce the incidence of postoperative pain and the degree of impairment in respiratory function. Frazee et al. showed that the postoperative decrease in vital capacity reached 52% of preoperative value after laparotomy and 73% after laparoscopic cholecystectomy (55). Putensen-Himmer et al. found similar results, with an even lower decrease in FRC after laparoscopic surgery (56). However, PPC after laparoscopic surgery has been shown to occur in 0.07% of patients (1 in 1518 cases). No comparative study has been done with conventional cholecystectomy (57). The incidence of PPC after cholecystectomy by laparotomy was reported in previous studies to be around 0.8% (8 pneumonias in 1035 cases) (58). Furthermore, recent preliminary data suggest that the duration and the severity of diaphragm dysfunction might be less pronounced after laparoscopic cholecystectomy than after conventional cholecystectomy (59).

However, if the postoperative course of laparoscopic surgery may induce less respiratory disturbance, the intraoperative consequences may be more important than for laparotomy. The respiratory load induced by increased intraabdominal pressure regularly requires the use of intubation and mechanical ventilation. The usual effects on gas exchange are an increased dead-space ratio, inducing a marked increase in the alveolo-arteriolar $CO_2$ gradient, which must be evident in the interpretation of end-tidal $CO_2$ monitoring (60). Intraoperative hypoxemic episodes have been reported but are rather rare (61,62). They would be major indications to interrupt laparoscopic surgery.

Therefore, the choice between laparotomy and laparoscopic surgery cannot rely on the results of comparative studies. However, when this technique is possible and when major alterations in gas exchange do not occur intraoperatively, laparoscopic surgery in COPD patients may be beneficial because it causes less postoperative alterations of respiratory function.

### D. The Postoperative Period

Beyond general prophylactic maneuvers such as postoperative analgesia and early ambulation, respiratory physiotherapy has been shown to be most effective in preventing the development of PPC (63–65). Several prospective studies have

shown that the incidence and severity of PPC can be reduced by respiratory maneuvers that tend to increase lung expansion. These different techniques should be learned and practiced by the patients before surgery, when they are more attentive and free of pain, rather than during the postoperative period. The efficacy of these respiratory maneuvers has been shown in numerous studies. Thorens showed in patients undergoing elective cholecystectomy in 1954 that physiotherapy, including hourly breathing exercises and postural drainage, reduced the incidence of PPC from 30 to 12% (64). More recently, Morran et al. confirmed these results in a prospective randomized study of 102 patients undergoing cholecystectomy (66). Physiotherapy, consisting of breathing exercises and assisting coughing, reduced the incidence of postoperative chest infection from 38% in the nontreated group to 14% in the treated group.

Different techniques may be used. As pointed out by Celli, the methods used in the past were essentially expiratory maneuvers (blow-bottles, expiratory resistance), while most of the methods currently used (incentive spirometry, IPPB, deep breathing exercises) are inspiratory and aim at increasing inspiratory lung volume (67). Inspiratory methods of physiotherapy try to expand lung volume, either by spontaneous recruitment of a reflexly inhibited diaphragm, as with incentive spirometry or deep breathing exercises, or by a passive inflation obtained by IPPB. All these physiotherapy techniques reduce the incidence of PPC, but few have shown marked differences in efficacy (68). IPPB is no more effective than incentive spirometry but is associated with a higher incidence of abdominal distention and discomfort. It may be useful in patients with poor cooperation or restrictive neuromuscular disease.

Incentive spirometry offers the advantage of giving some feedback about the inspiratory effort achieved by the patient. It is inexpensive and has been shown to be as effective as other physiotherapy methods (69). Deep-breathing exercises, including inspirations to total lung capacity, were shown to reduce postoperative hypoxemia (69). CPAP has also been used during the postoperative period as an aid to lung expansion. Ricksten et al. showed that improvements in FVC and oxygenation in the patients receiving intermittent CPAP are similar to those seen in patients treated with incentive spirometry (70).

Expiratory maneuvers frequently used in the past are being abandoned in favor of inspiratory maneuvers. Although they might theoretically induce a reduction in lung volume and could produce lung collapse, they were nevertheless shown to reduce the incidence of PPC. This was probably the consequence of the deep inspirations taken before the expiratory effort. Furthermore, among expiratory maneuvers, coughing at the end of deep inspiration helps to clear retained secretions and was shown to be a most effective maneuver (64).

Some studies have suggested that pharmacological approaches could be useful in improving diaphragm activity. Aminophylline was shown to prevent respiratory muscle fatigue and to improve diaphragmatic function in the post-

operative period of upper abdominal surgery (71,72). However, its use is still controversial, since it also has an inotropic effect on respiratory muscles, which may increase respiratory work and lead to respiratory muscle fatigue and respiratory failure (29). Furthermore, its therapeutic index is narrow (71,72). Corticosteroids used in obstructive patients decrease respiratory load and may be beneficial (73). Malnutrition and hypophosphatemia should be corrected when necessary.

Another interesting approach is the administration of an extradural thoracic block, which was shown to restore preoperative indexes of diaphragmatic activity. However, this technique is associated with the motor blockade of the abdominal muscles. Although this motor block could be beneficial in preventing the decrease in FRC induced by expiratory abdominal muscle contraction, it could also be deleterious by decreasing cough, which is essential for clearing bronchial secretions after surgery in COPD patients. Different studies have shown that epidural anesthesia during the postoperative period is effective for improving the comfort of the patients and is helpful for an effective practice of physiotherapy. However, this technique does not decrease the incidence of PPC (13,74).

## V. Conclusion

The perioperative period has been shown for years to be a time of high risk for patients with COPD undergoing upper abdominal or thoracic surgery. The understanding of postoperative respiratory changes had progressed but does not yet lead to clear clinical conclusions concerning the management of these patients during the postoperative period. Although upper abdominal, thoracic, and cardiac surgery probably induce a reflex decrease in diaphragmatic activity during the postoperative period, the role played by the contraction of the abdominal muscles has still to be clarified.

The management of these patients relies on a good evaluation of the respiratory status of the patients, the prevention of intraoperative bronchospasm, the judicious choice of a surgical technique, and an effective practice of the techniques of postoperative physiotherapy, which remains the major therapeutic maneuver clearly shown to decrease the incidence of postoperative pulmonary complications. Although postoperative pain probably is not the main determinant in the development of postoperative complications, pain relief, by allowing postoperative physiotherapy to be more effective, should be more frequently offered in association with an active program of physiotherapy when patients can be monitored carefully.

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# 18

# The Role of Bronchoconstriction During Acute Respiratory Failure of Chronic Obstructive Pulmonary Disease

## Bronchodilators and Corticosteroids

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## I. Introduction

Definitions of chronic obstructive pulmonary disease (COPD) often include irreversibility with a lack of response to bronchodilator therapy. However, most patients experience intermittent worsening of their symptoms with acute episodes of cough, wheezing, and dyspnea. Many persons with so-called "irreversible" obstructive lung disease show significant bronchodilation after a single dose of an inhaled bronchodilator (1,2), while bronchoconstriction can result from the inhalation of exogenous irritants, such as cigarette smoke. The rapid onset and resolution of these changes in airway caliber might suggest that they are the result of smooth muscle contraction and relaxation (3).

The underlying pathophysiology in patients with COPD varies, with variable components of bronchitis, emphysema and airway hyperresponsiveness (4). Overlapping clinical features make it difficult to classify patients on clinical grounds. Laennec was the first to describe airways obstruction as a feature of emphysema (5). Chronic airflow obstruction can result from lesions in central airways, peripheral airways or lung parenchyma, and the lesions often occur together (6,7).

A reduction in airways caliber with increased airway resistance can be

attributed to airway inflammation (8), increased airway mucus, and bronchoconstriction by smooth muscle shortening (9). The causes for acute respiratory failure (ARF) in patients with COPD are numerous, and it may be extremely difficult to recognize a single cause for potential reversible respiratory decompensation (10). Common precipitating conditions are infections, pulmonary embolism and left ventricular failure (11). ARF is primarily characterized by an increased resistive load on the respiratory muscles (11) due to increased flow resistance (12). Decrease of the load, therefore, is one of the major goals of therapy because of the impending fatigue of the respiratory muscles.

In asthmatic patients smooth muscle contraction and inflammation are generally considered prominent mechanisms of increased airways obstruction; therefore therapy with bronchodilators is indicated. However, in COPD patients, the role of smooth muscle tone in causing airways obstruction is still the subject of controversy, despite a large number of publications. Reported results range from detrimental effects of bronchodilator therapy (13) to dramatic improvement in measures of airway obstruction in subsets of patients (14). Bronchospasm was thought to be a component of respiratory decompensation in most ARF episodes in patients requiring mechanical ventilation (15). Treatment with corticosteroids directed at the inflammatory component of airways obstruction is also controversial (16). In patients with severe COPD and a low ventilatory reserve, it is of major importance to establish an appropriate diagnosis and to administer a rational therapy directed at the reversible part of airflow obstruction.

## II. Airway Narrowing and Airway Responsiveness

The role of increased responsiveness of airways in the pathogenesis and perpetuation of COPD is still under discussion. Morphologically increased amounts of airways muscle can be present in patients with COPD (9), and it could be assumed that this reflects airway hyperreactivity in chronic obstruction. However, in a study based on the examination of the lungs of patients who died during the National Institutes of Health clinical trial of Intermittent Positive Pressure Breathing, Nagai and coworkers found no relationship between central airway muscle and airflow reversibility (7).

Even in patients with far-advanced emphysema and chronic bronchitis with airways critically narrowed by the loss of parenchymal elasticity, increased endobronchial secretions, and bronchial wall thickening, the tracheobronchial tree preserves it ability to alter caliber to a measurable degree airway through smooth muscle activity (3). Bronchial hyperresponsiveness can be defined as the sensitivity of the airways to a spectrum of nonsensitizing stimuli of chemical or physical origin (17). An increase in airway responsiveness to methacholine or histamine in patients with COPD has been well documented (18–21). Patients

with COPD tend to be less responsive than asthmatic patients, with different shaped dose-response curves, but tests of bronchial hyperreactivity with methacholine or histamine cannot be used to distinguish COPD from asthma, as shown in Figure 1.

However, there are differences between the airway hyperresponsiveness in patients with asthma and those with COPD. Woolcock and coworkers, who studied a number of different provoking stimuli in patients with mild COPD, concluded that in these patients the airways narrow too easily and perhaps too much, but they responded only to some provoking stimuli (21). Differences are outlined in Table 1.

The maximal response may differ between patients with asthma and those with COPD. Patients with mild COPD do not seem to be able to increase their degree of obstruction in response to acute stimuli. Challenge studies to maximal response have not been done in patients with severe COPD because they are not safe. There is an inverse relationship between prechallenge pulmonary function level and degree of methacholine and histamine responsiveness in patients with COPD (23,24), while this relationship is less clear in asthmatics (23).

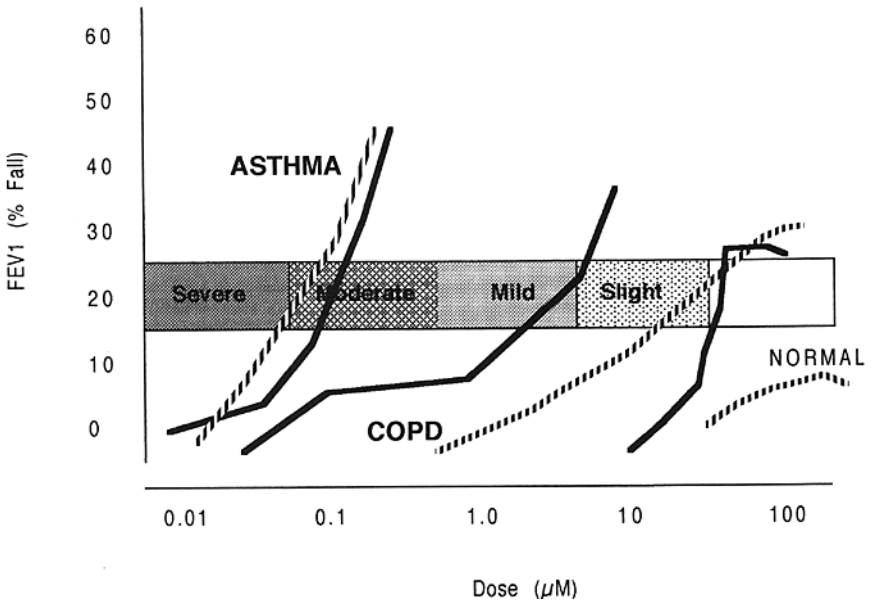


**Figure 1** Typical dose-response curve to histamine (solid lines) and methacholine (dashed lines) in an asthmatic, a COPD, and a normal subject. (Adapted from Ref. 21.)

**Table 1** Differences in Airway Responsiveness Between Asthma and COPD

| Bronchoconstricting stimulus | Asthma | COPD |
|---|---|---|
| Histamine, methacholine | | |
| Response | ++ | + |
| Dose-response plateau | − | + |
| Relation to reduced $FEV_1$ | + | +++ |
| Cold air hyperventilation | + | − |
| Methoxamine | + | − |
| Propanolol | + | − |
| Distilled water | + | − |
| Polymyxin b | + | − |

*Source*: Ref. 22.

Several morphologic factors may contribute to the relationship between prechallenge pulmonary function level and degree of responsiveness (25,26). Since resistance is inversely proportional to the radius of the airway to the fourth power according to Pouseuille's law, a reduction in airway radius leads to a proportionately greater increase in resistance to flow when the initial size of the airways is smaller. Any given baseline airway constriction also alters the position of the smooth muscle on its intrinsic length-tension curve (27). As the airway narrows, an exponentially smaller amount of smooth muscle shortening is required for the same change in flow (26). Therefore a narrowed airway with a thickened wall would decrease the $FEV_1$ and give an enhanced response (21), even though bronchial smooth muscle may contract normally in response to a stimulus.

Pulmonary emphysema with impaired tractional support of the bronchial wall and abnormal bronchial collapsibility is a common pathological finding in patients with COPD. Nagai and coworkers reported it to be the major morphological correlate of airflow obstruction in patients dying with moderate to severe airflow obstruction (7). Loss of elastic recoil would increase airway responsiveness because of the decreased load against which the muscle works during bronchoconstriction (28,29). Additionally, the way in which responsiveness is expressed influences the magnitude of response and is not independent of the baseline lung function (30,31).

The responses to a bronchoconstricting and a bronchodilating stimulus can be independent of each other. Ramsdall and coworkers showed that even in patients with no reversibility of airflow obstruction during bronchodilator therapy, a constrictive effect occurred with methacholine challenge, and this bronchoconstriction was reversed after inhalation of isoproterenol (32). Postma and cow-

orkers found that the annual rate of decline in lung function was highest in patients with chronic obstructive bronchitis with increased nonspecific hyperreactivity and decreased reversibility to bronchodilators (33). Among patients with established chronic obstructive airways disease, evidence of an asthmatic-bronchitic type of disease such as responsiveness to bronchodilators and improvement with corticosteroids has been associated with a good survival rate and a slow progression of impairment (34).

In COPD the airway smooth muscle may be normal with normal mediator-releasing cells; the hyperresponsiveness to histamine and methacholine would then be only due to airway geometry. Increased airway responsiveness and decreased pulmonary function might also be due to chronic airway inflammation. Bronchiolar inflammation is an early and persistent lesion in smokers (9). It could be related to airway obstruction by the effects of inflammatory mediators on vascular, secretory, and smooth muscle function. A correlation between histological inflammation in membranous bronchioles and the methacholine dose producing a 20% fall in forced expiratory volume in 1 second (FEV1) ($P_{CO_2}$) has been found in patients with COPD (35). The superoxide generation of polymorphonuclear leukocytes in peripheral blood in patients with COPD as an activity parameter of inflammatory cells was inversely related to the $P_{CO_2}$ (36).

Bronchial hypersensitivity and excessive airway narrowing are multicausally determined in COPD, making it difficult to offer a rational therapeutic plan when the causes of the disorder remain unknown (37).

## III. Bronchodilators

The rationale for bronchodilator therapy in COPD has often been questioned (13,38). There is still no evidence that long-term administration of bronchodilators has any influence on the natural history of stable chronic airflow obstruction. Although it is presumed that bronchospasm is partly responsible for the acute ventilatory deterioration in exacerbations of COPD, its precise role is not known, and other mechanisms relating to bronchial inflammation and retained secretions may be more important. However, bronchodilators remain the mainstay of treating acute exacerbations of COPD in addition to supplemental oxygen and measures to improve bronchial toilet and support of respiratory muscles. Patients are usually treated with inhaled bronchodilators but not always with parenteral theophylline (39). Most patients with ARF are treated empirically, since response to therapy often is not documented to lung function measurements in unstable or ventilated patients. Even small improvements in airway resistance can be of significant benefit (11), particularly if they reduce the effort of breathing by decreasing gas trapping and hyperinflation. Several classes of agents with bronchodilator effects, including theophylline, $beta_2$-adrenergic agonists, anticholinergics, and glucocor-

ticoids, are commonly used in COPD. Numerous studies have investigated the efficacy of these bronchodilators, but results are conflicting due to differences in patient populations, duration and dosage of therapy, and measurements of outcome. Patients who do not show a response to one bronchodilating agent may have a significant response to another bronchodilator, and single-drug therapy has been shown to achieve maximal bronchodilation in many COPD patients (40), while other investigators found additive effects for two or more bronchodilators (41,42). Additionally there is a marked intraindividual day to day variability in bronchodilator responsiveness (43). There are only few studies in patients with ARF of COPD; most data have been obtained from patients in so called stable state of disease.

### A. Theophylline

The role of theophylline in the management of obstructive lung diseases remains the subject of controversy (44–47). It was used as a first-line drug in the treatment of chronic obstructive airways disease for decades, with its presumed mode of action being the inhibition of degradation of 3':5'-cyclic adenosine monophosphate (cAMP) by phosphodiesterases in smooth muscle cells. However, the effects of theophylline on the different forms of phosphodiesterases are not yet completely known (48). Other mechanisms of action for the bronchodilator effect of theophylline have been proposed including changes in the calcium channel, inhibition of histamine and leukotriene release from mast cells, inhibition of adenosine receptors, and interference with the effects of prostaglandins on smooth muscle. Theophylline has respiratory effects other than bronchodilation that are of relevance to the management of patients with COPD (49). Therapeutic effects include stimulation of ciliary beat frequency and better mucocilliary clearance (50), enhanced right and left ventricular performance (51), stimulation of the central nervous system and respiratory center (52), and increased diaphragmatic contractility (52). Therefore the effects of theophylline on respiratory function will depend on the relative contribution of each of these factors in individual subjects (11).

In recent years, theophylline has been used as a second- or third-line therapy in COPD, since it is a relatively weak bronchodilator compared with $\beta_2$-agonists or anticholinergics (53,54). It is commonly used to treat "irreversible" airflow obstruction, but patient benefit is not firmly established, and its clinical efficacy in ARF of patients with COPD has not been undoubtedly proven.

Little information is available about the value of theophylline in acute exacerbations of COPD. Rice and coworkers were unable to show that the administration of parenteral aminophylline provides significant additional benefits when added to treatment with metaproterenol in hospitalized patients with exacerbation of COPD (55). In a retrospective analysis over a 4-year period, it was

found that intravenous aminophylline given to patients with decompensated COPD with serum theophylline levels less than 10 mg/liter was associated with a significantly increased 48-hour relapse rate. It was concluded that aminophylline does not appear to be beneficial for outpatients with decompensated COPD and may be harmful (13,56). However, Wrenn and coworkers found that additional treatment with intravenous aminophylline and a mean achieved theophylline concentration of 9.7 mg/liter significantly decreased hospital admission rate compared to placebo (6% vs. 21%) in 134 patients with moderate to severe acute exacerbations of asthma or chronic obstructive pulmonary disease, who were treated with high-dose inhaled $\beta_2$-mimetics and parenteral glucocorticosteroids in the emergency room. This was an unexpected finding, because the addition of aminophylline had little effect on pulmonary function (57). The same result was found when the subgroup of patients with COPD was analyzed separately; 7% of aminophylline-treated but 26% of placebo-treated COPD patients were admitted.

Single-dose administration of theophylline was associated with dose-dependent improvement in ventilatory function in patients with "irreversible" airflow obstruction, but subjective relief of dyspnea was not demonstrated (58). In patients with stable COPD, high doses of inhaled salbutamol produced more bronchodilation than theophylline alone, but a small additive effect can be found when both agents are used (59). McKay and coworkers showed an improvement in peak flow, trapped gas volumes, and walking distance by theophylline treatment with high steady-state concentrations of about 17 mg/liter when it was added to bronchodilators and corticosteroids (60). In 60 patients with severe COPD theophylline, treatment for 2 months led to a significant improvement in pulmonary gas exchange and a 13% average increase in $FEV_1$. This was only partly attributed to bronchodilation and thought to be partly due to the improvement of respiratory muscle performance of approximately 29% (61).

In 38 clinically stable patients with severe COPD, withdrawal of theophylline therapy resulted in significant deterioration in lung function, exercise performance, and two indices of overall dyspnea and a significant increase in scoring of symptoms and auscultation findings (62). Individual analysis revealed a clinically relevant deterioration in 72% of patients from whom theophylline therapy was withdrawn, while only 15% of patients receiving theophylline deteriorated. Kirsten and coworkers, (62) concluded that about half of the patients with severe COPD can be considered as "theophylline responders."

Other investigators found that in patients with COPD with advanced but stable airway obstruction, the drug may significantly relieve dyspnea without simultaneous improvement in lung function tests or exercise performance (63). Several other studies have shown significant benefits from theophylline in severely impaired patients with COPD (64,65). Mulloy and McNicholas (66) found that oral theophylline significantly improved gas exchange during rest, exercise, and sleep in 10 patients with severe but stable chronic obstructive pulmonary

disease who were continued on their usual bronchodilator therapy. Theophylline resulted in a small but significant additional improvement in pulmonary function and reduced trapped gas volume (66).

#### *Adverse Effects*

A deterioration in pulmonary gas exchange after administration of aminophylline was first reported by Halmagyi and Cotes (67) and later confirmed by others (68). The suggested mechanism was partial inhibition of hypoxic pulmonary vasoconstriction by the drug. Barberá and coworkers assessed the effect of intravenously administered aminophylline on the distribution of ventilation and perfusion in patients with COPD recovering from acute episodes of respiratory failure and compared its effect with that of 100% $O_2$ breathing (69). In these patients aminophylline alone caused significant improvement in forced spirometry, which continued to improve when aminophylline and 100% $O_2$ were given simultaneously. They found that short-term intravenous administration of aminophylline had no effect on $\dot{V}_A/Q$ relationships for the whole group, but $O_2$ treatment alone or in combination with aminophylline worsened $\dot{V}_A/Q$ mismatch (69). Individual patients with substantial low $\dot{V}_A/Q$ areas at baseline showed moderate deterioration in their $\dot{V}_A/Q$ distributions in response to the drug, which was thought to be of little clinical significance.

Therapy with theophylline requires close monitoring because of the high frequency of side effects and the narrow therapeutic window with possible toxic effects at serum concentrations close to the upper therapeutic range (70). A high interindividual variability of clearance with changing theophylline disposition in acutely ill patients makes the plasma theophylline concentration resulting from any dosage relatively uncertain (71). The likelihood of a therapeutic benefit and the safety of drug therapy can be increased markedly by an individually optimized theophylline therapy with individual dosage and monitoring of serum concentrations (46).

#### *Place in Therapy*

The present findings provide evidence of a significant benefit from theophylline in many patients with advanced COPD. The clinical effectiveness of this drug cannot be explained exclusively by its moderate action on airway obstruction (72). Since it is difficult to predict response to theophylline, its effectiveness in patients with severe COPD should be determined individually.

### B. $\beta_2$-Adrenergic Agonists

The $\beta_2$-adrenergic agonists are the most frequently used bronchodilators in the treatment of COPD. Stimulation of $\beta_2$-receptors on airway smooth muscle leads to

relaxation by activation of adenyl cyclase. Additionally, $\beta_2$-adrenergic agonists have been demonstrated to improve mucocilliary clearance (73) and to increase inspiratory muscle endurance time (74). Furthermore, they improve systolic ventricular function, predominantly by decreasing pulmonary and systemic vascular resistances in patients with severe COPD.

Parenteral, oral, and inhalational forms are available. The inhalational route, however, should be used because its use results in greater bronchodilation and fewer side effects at low doses. Aerosols may be administered with metered dose inhalers (MDI) or by compressor-generated nebulizers. In patients with severe COPD, high-dose treatment by nebulizer can frequently be used with good bronchodilator response (75). In intubated, mechanically ventilated patients, Manthous and coworkers did not find any significant effect on airway resistance after albuterol delivered by MDI in cumulative doses of 100 puffs (9 mg) through an endotracheal tube. By contrast, administration of albuterol by nebulizer at cumulative doses of 7.5 mg significantly reduced the inspiratory flow resistive pressure but led to toxic side effects in 4 out of 10 patients (76). The authors concluded that albuterol was not delivered to the patient by MDI with their technique, which is commonly used in clinical practice. However, Fernandez and coworkers showed in 20 intubated patients with ARF of COPD that the administration of 0.2 mg salbutamol by MDI through a special adapter with slow bag–delivered inflations produced a significant bronchodilation, avoiding the risk of nosocomial infection (77).

The dosing requirements for patients with COPD have not been well evaluated, and most recommended doses result in less than maximal bronchodilation (78). The response has been shown to be dose dependent in stable COPD patients (79, 80). Several studies have found that the acute response to an inhaled bronchodilator does not predict the patient's long-term response to $\beta_2$-sympathomimetics (81–83).

Peacock and coworkers (84) evaluated four different inhaled $\beta_2$-adrenergic agonists in 18 patients with stable COPD. Acute bronchodilator response was not significantly different between the four agents, with a mean change of 27–31% of prebronchodilator $FEV_1$. Each patient received treatment with the greatest or least response–invoking agent for 4 weeks, followed by a second interval with the opposite agent. Use of the greatest response-invoking agent resulted in improvement of baseline pulmonary function with significantly larger prebronchodilator and postbronchodilator $FEV_1$ (84).

Anthonisen and coworkers (2) measured response to 250 μg isoproterenol in 985 patients with COPD and followed the patients for nearly 3 years with continued bronchodilator therapy. Initial response averaged 15% of the baseline (Fig. 2). Patients with large absolute and relative bronchodilator responses had slower rates of decline in lung function than less responsive patients (Fig. 3). There was a tendency for bronchodilator response to diminish with time, which

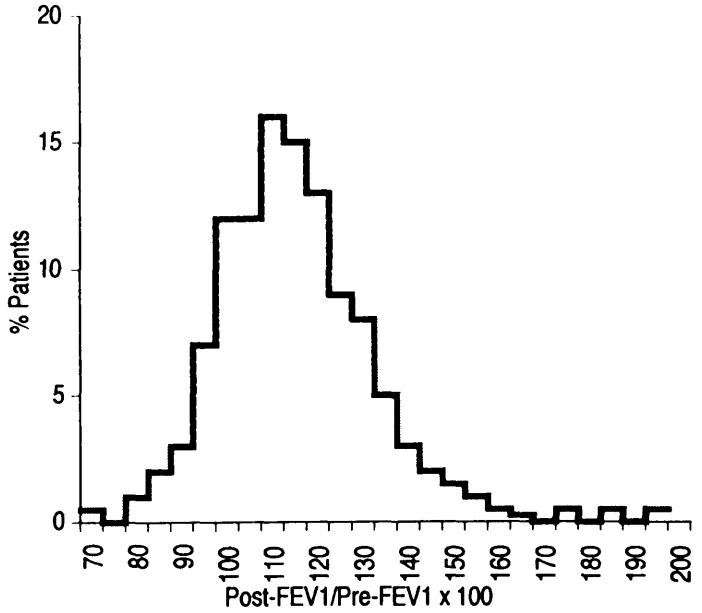


**Figure 2** Frequency distribution of relative bronchodilator response. Ordinate: % of patients. Abscissa: Bronchodilator response expressed in terms of postbronchodilator $FEV_1$ as a percentage of the prebronchodilator $FEV_1$. (Adapted from Ref. 2.)

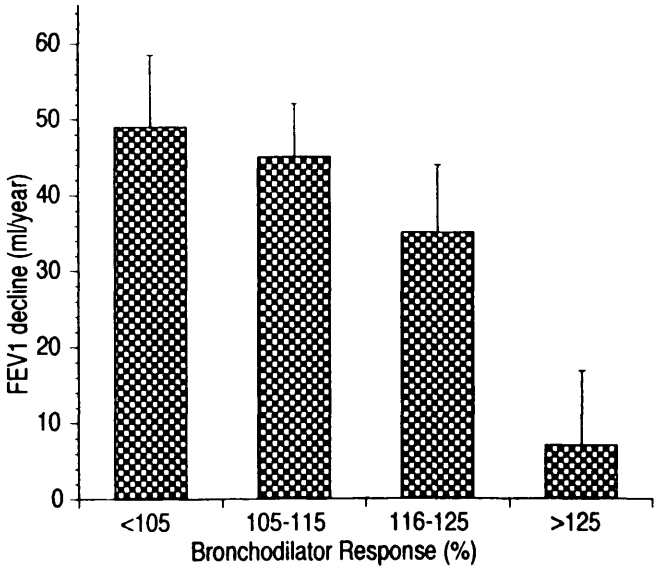


**Figure 3** Bronchodilator response (post-$FEV_1$/pre-$FEV_1$, %) and yearly decline in $FEV_1$ (ml ± SEM). (Adapted from Ref. 2.)

might be interpreted as evidence of tachyphylaxis or as a reflection of the gradual decline in $FEV_1$ with disease progression. There were large time-related interindividual and intraindividual variations of response. Therefore the authors concluded that response to a bronchodilator with resulting therapeutic decisions should not be assessed on the basis of a single test (2).

Guyatt and coworkers (82) found a similar lack of reproducibility of bronchodilator response in 24 patients with COPD. However, most patients had symptomatic benefit from either albuterol (14 patients), theophylline (12 patients), or additional benefit from simultaneous administration of both drugs (8 patients), while 5 patients did not respond to either drug. The mean response to inhaled albuterol did not relate closely to symptomatic response to either albuterol or theophylline and therefore was not a useful parameter for identifying patients likely to benefit from bronchodilator treatment (82).

In mechanically ventilated patients with COPD, Gay and coworkers found that inhalation of 1.8 mg metaproterenol led to a reduction in peak pressure and auto-PEEP in 10 of 13 patients, which was interpreted as a significant bronchodilator response (85). In 20 mechanically ventilated patients with ARF of COPD, Fernandez and coworkers separately assessed the therapeutic effects of intravenous theophylline and of ipatropium bromide (0.04 mg) and salbutamol (0.2 mg) given by metered dose inhaler to the endotracheal tube. With all three drugs, airway pressures and auto-PEEP were reduced, while a significant increase in compliance was only observed after salbutamol (77). Bernasconi and coworkers found in 7 ventilated patients with ARF of COPD that a dose of 0.4 mg of inhaled salbutamol was followed by a rapid and significant decrease in maximum and minimum respiratory resistance ($-33\%$ and $-28\%$) and PEEPi ($-44\%$) with a slight but not significant further fall with higher doses (86).

### *Adverse Effects*

The most common side effects of $\beta_2$-adrenergic agonists are tremor, tachycardia, and nervousness. There has been some concern about the safety of $\beta_2$-adrenergic agonists in asthmatics and the development of tolerance to these agents (87,88). $\beta_2$-Receptor downregulation develops rapidly after exposure with $\beta_2$-adrenergic agonists in vitro and on peripheral lymphocytes, however, no significant change in bronchodilator response has been shown in asthmatics (87,89). Recent research has shown the development of tolerance to nonbronchodilator effects of $\beta_2$-agonists with loss of protection against some constrictor stimuli in asthmatics (90) and a small increase in bronchial responsiveness (87). In COPD patients there are almost no data available about these effects so far.

Georgopoulos and coworkers found in patients with COPD that continuous long-term administration of $\beta_2$-adrenergic agonists decreases the duration of bronchodilation but does not affect the peak response, suggesting the development of some degree of tolerance to $\beta_2$-adrenergic agonists (91). A decrease in the arterial oxygen tension can be observed after inhalation of $\beta_2$-adrenergic agonists

(86,92). Explanations for this effect include reversal of hypoxemia-induced pulmonary vasoconstriction or an increase in cardiac output with increased perfusion of hypoventilated areas of the lung (93). It can be controlled by oxygen administration (86).

#### *Place in Therapy*

$\beta_2$-Adrenergic agonists are efficacious in the treatment of acute exacerbations of COPD and should be used as first line therapy.

### C. Anticholinergics

Quaternary anticholinergic agents have been shown to be more effective in patients with COPD than in those with asthma, although the reason for this is not completely clear (94). In stable COPD patients the efficacy of anticholinergic drugs has been reported as superior to sympathomimetics by some investigators (95–97), and others have reported that these agents are synergistic when used together (98). However, this might be due to submaximal doses of one or both agents (99). In patients with stable COPD, anticholinergic agents are recommended as first-line treatment (100). Whether anticholinergic drugs are indicated in ARF of COPD patients remains to be established.

In acutely ill COPD patients, Karpel and coworkers showed similar improvements in pulmonary function after ipratropium bromide or metaproterenol sulfate with significant improvement in $FEV_1$ of 24% versus 18% with no further change after crossover (study 1) (101). In the same subjects there was significantly less airway obstruction at stable state of disease (study 2), with the response to ipratropium (54 μg) and metaproterenol (1.95 mg) being significant and similar to study 1 without improvement after crossover (102) (Fig. 4).

Similar results for stable COPD patients have been reported by Easton and coworkers with higher doses of salbutamol (600 μg) or ipratropium (120 μg) (99) and in patients with emphysema by Gross and Skorodin (103). It can be concluded from these data that the sympathomimetic and anticholinergic agents are comparable in their bronchodilatory properties, but that stable patients given therapeutic doses of $\beta_2$-agonists rarely benefit from the addition of an anticholinergic agent (104). Ohrui and coworkers showed by use of an intrabronchial catheter that inhaled atropine sulfate acted predominantly on the central airways, while fenoterol dilated both the central and peripheral airways in patients with COPD (105).

Gross and Bankwala compared the effect of atropine methonitrate and metaproterenol inhalation on gas exchange in 12 patients with COPD. They found no significant decrease in $Po_2$ with atropine but showed a mean decrease in $Po_2$ of 5.0 ± 2.5 mmHg (92). Karpel showed in patients with acute exacerbations of COPD that metaproterenol resulted in an initial deterioration in gas exchange, while ipratropium resulted in a small, but significant improvement in gas exchange (101).

In 21 patients with stable COPD, $FEV_1$ increases over baseline and the

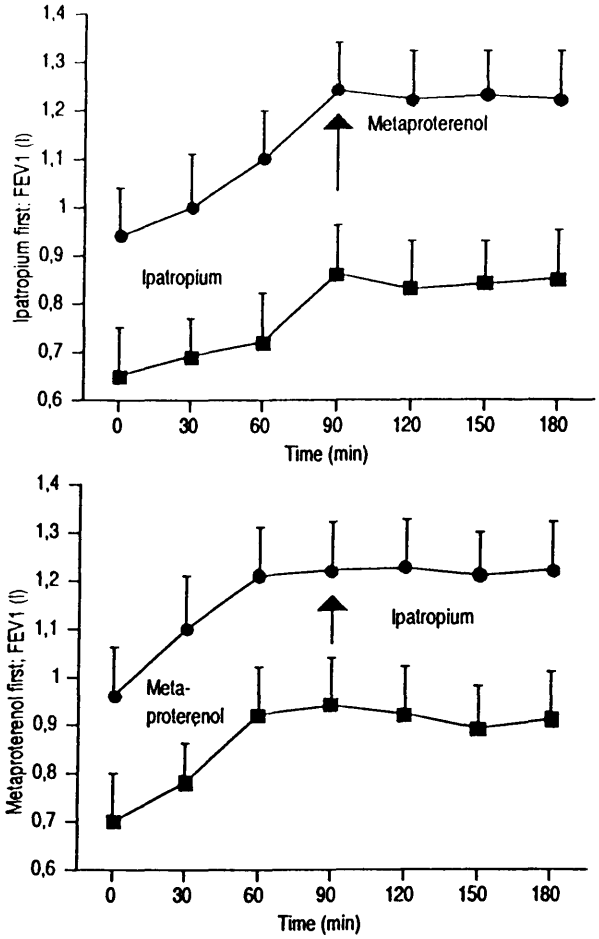


**Figure 4** Changes in $FEV_1$ vs. time from patients with COPD during acute exacerbations (circles) and while stable (squares) (a) following sequential inhalation of ipatropium (54 μg) and metaproterenol (1.95 mg) or (b) the reverse sequential inhalation of metaproterenol (1.95 mg) and ipatropium (54 μg). (Adapted from Ref. 102.)

proportion of patients attaining at least a 15% increase in $FEV_1$ (responders) was significantly higher in patients treated with ipratropium than in those treated with oral theophylline (106).

In stable COPD patients anticholinergic agents should be used as first-line therapy because of their wide margin of safety and proven bronchodilator efficacy. For acute situations $\beta_2$-agonists may be preferred because of their faster time to peak effect (54).

## IV. Corticosteroids

In patients with COPD the administration of corticosteroids remains subject to discussion despite more than 40 years of clinical use and investigation (107,108) and an established role in the treatment of acute asthma (109). Corticosteroids have many pharmacological effects that could be beneficial for patients with decompensated COPD when bronchospasm or excessive inflammation is present. They modify the inflammatory response, inhibit the release of inflammatory mediators, and prevent tachyphylaxis to chronic adrenergic stimulation (110,111).

However, it has been difficult to prove that patients with stable or decompensated COPD benefit from steroid treatment (16). In stable COPD patients, long-term studies have reported improvement in subsets of patients (112–114), while other studies have shown negative results (115,116). Weir and Burge showed that inhaled beclomethasone diproprionate produced a small but significant improvement in $FEV_1$ in patients with stable COPD. The addition of oral prednisolone did not produce further improvement. No improvement in bronchial responsiveness was detected after 6 weeks of treatment (117).

Wempe and coworkers showed in 10 patients with COPD that short-term treatment with inhaled or oral corticosteroids does not modify the bronchodilator response to salbutamol or ipatropium bromide or the protection provided by either drug against histamine (118). In 100 patients with stable COPD, Nisar and coworkers (119) measured response to either 5 mg of nebulized salbutamol or 500 μg of nebulized ipatropium bromide and repeated spirometry after treatment with 30 mg of oral prednisolone for 2 weeks. They found that 67 patients responded to salbutamol and/or ipatropium bromide with an increase in $FEV_1$ of at least 15%. Most of the 22 patients who improved after corticosteroids showed a positive bronchodilator response to salbutamol (90% specific) or ipatropium bromide (84% specific).

It is still unclear whether or not corticosteroids improve the prognosis of acute failure. Emerman and coworkers found that a single dose of 100 mg methylprednisolone had no effect on $FEV_1$, the hospitalization rate, or the 48-hour relapse rate for patients treated in an emergency department (109). However, Murata and coworkers (56) found that a regimen of intravenous and oral corticosteroids significantly reduced the relapse rate after treatment of decompensated COPD. In 30 patients, 45 emergency department visits in which intravenous and oral corticosteroids were given were compared with an equal number of matched visits in which the drugs were withheld. At 48 hours after discharge, the cumulative relapse rate for visits after corticosteroid treatment was 8.9% compared to a relapse rate of 33.3% for visits without corticosteroid treatment.

Albert and coworkers showed in a randomized clinical trial that hospitalized patients with ARF given intravenous methylprednisolone every 6 hours for 72 hours had greater improvement in $FEV_1$ than those given placebo (120). In mechanically ventilated patients with ARF of COPD, Rubini and coworkers found

that intravenous administration of 0.8 mg/kg methylprednisolone induced a significant decrease in inspiratory resistance and dynamic hyperinflation (121). The authors concluded that treatment with corticosteroids improves respiratory mechanics, providing better conditions for weaning from mechanical ventilation.

Corticosteroids have numerous adverse reactions, including impairment of respiratory and skeletal muscle function, endocrine disturbances, psychiatric disorders, and gastric bleeding, but these complications occur mainly during chronic treatment (111,122).

The available data provide evidence that systemic corticosteroids are indicated in patients with ARF of COPD when severe bronchospasm or excessive inflammation is present.

## V. Conclusion

Acute respiratory failure of COPD with fatigue of respiratory muscles can be caused by numerous factors (11). It is of critical importance to identify causes for potential reversible respiratory decompensation. Bronchospasm is a component of the respiratory decompensation in most ARF episodes in patients requiring mechanical ventilation (15). Inflammation of the airways additionally contributes to severe airway obstruction. Patients with COPD usually do not respond dramatically to bronchodilator therapy. However, even small decreases in airway resistance may be important for achieving recompensation. Therefore a rational pharmacotherapy directed at improving airflow is necessary for decreasing the load on the respiratory muscles. Depending on the individual responses therapy with sufficient doses of $\beta_2$-adrenergic agonists, theophylline, and systemic corticosteroids should be used in acute severe exacerbations.

Few studies have investigated the value of bronchodilator and corticosteroid therapy in patients with ARF of COPD (55,56,86,120,121). Further carefully designed controlled studies addressing questions of dosing and ways of drug administration, use of single drug or multidrug bronchodilator therapy, and preventive therapy are needed.

## Acknowledgement

This paper is dedicated to Fritz Hartmann on the occasion of his 75th birthday.

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# 19

# Nutritional Evaluation and Therapy During Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

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## I. Introduction

Nutritional impairment adversely affects numerous components of the respiratory system, including respiratory muscle function, metabolism and gas exchange, ventilatory drive, and host defense mechanisms. This knowledge has led clinicians to promote nutritional therapy as a major treatment goal for patients with respiratory failure including those with chronic obstructive pulmonary disease (COPD). Yet nutritional support places a ventilatory stress on a respiratory system already impaired by the disease process. Complications of nutritional support that can adversely affect outcome have been recognized. The appropriate use of nutritional support in the critical care setting requires a thorough knowledge of the interaction between nutritional status and the respiratory system.

The majority of research has focused on the more stable, emaciated COPD patient with predominant emphysema, examining the potential benefits of nutritional support in this setting. Less investigation has been conducted about skilled care of the COPD patient with respiratory failure. This chapter will address this latter population, including the influence of nutritional status on the underlying disease process and the potential role of nutritional assessment and therapy in the

treatment of the patient with COPD. Areas for future investigation will be highlighted.

## II. Pathophysiology of Respiratory Failure in COPD Patients

A more detailed description of the pathophysiology of respiratory failure and COPD is contained in other sections of this text. However, to understand the potential role of nutritional therapy in these patients, a few points are worthy of review.

Expiratory airflow obstruction is the cardinal feature of COPD exacerbations resulting from obstructive changes in the peripheral conducting airways (i.e., bronchitis) and/or destructive changes in the terminal respiratory bronchioles (i.e., emphysema). These morphological changes lead to the physiological equivalents of increased expiratory airflow resistance and reduced lung elastic recoil. The fixed rate of expiratory airflow significantly reduces the ventilatory reserve of these patients. COPD patients must increase either inspiratory flow rate or lung volume in response to heightened ventilatory demands. Either mechanism places a significant demand on the inspiratory muscles. As a result, the expiratory "mechanical load" of COPD results in adaptations that place a significant burden on the inspiratory muscles.

Efferent neural drive to the respiratory muscles is typically increased. The majority of COPD patients in acute respiratory failure, even in the presence of hypercapnia, demonstrate sustained levels of minute ventilation and higher respiratory control center output compared to more stable intervals (1).

This combination of high inspiratory workload and neural drive places a significant metabolic demand on the inspiratory muscles. In contrast to the normal subject, the COPD patient demonstrates a greater increase in energy requirements with small changes in minute ventilation (Fig. 1). At some point, the metabolic demand can exceed the energy supply to that muscle. At this point, respiratory muscle fatigue ensues. Respiratory muscle fatigue has been defined physiologically as the muscles lose the capacity to develop force and/or velocity in response to a load and the loss of force is reversible by rest (3).

Respiratory muscle fatigue has been documented under controlled laboratory conditions of inspiratory muscle loading (4). Fatigue during weaning from mechanical ventilation has also been suggested (5). However, the relationship between the onset of respiratory failure and fatigue in COPD patients is less definite (6,7). Much of the confusion in this area relates to the lack of precise definitions and simple methodology to identify specific fatigue states.

At the current time, respiratory muscle fatigue is best viewed as a continuous process rather than a single event (8). The process begins when the respira-

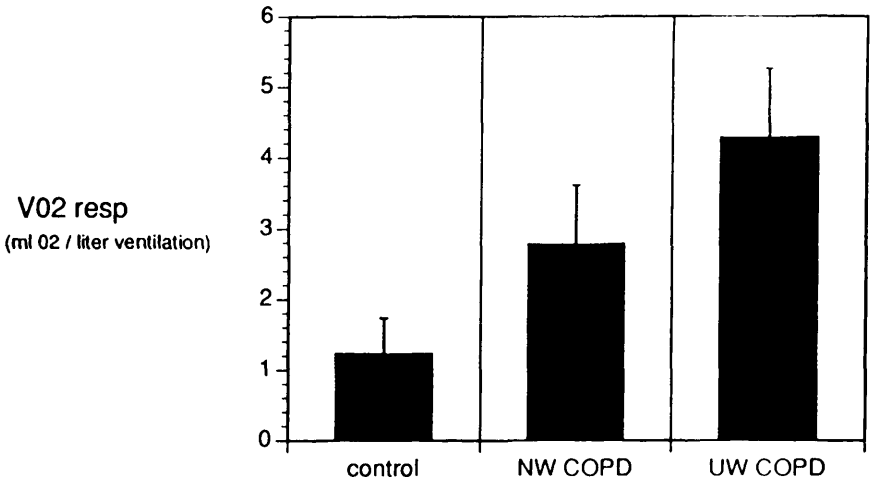


**Figure 1** Comparison of the metabolic cost of augmenting minute ventilation expressed as the change in $Vo_2$ per liter change in ventilation for controls, normal weight COPD patients and underweight COPD patients. Note the greater metabolic cost of augmenting ventilation for COPD patients in general and underweight COPD patients in particular. (From Ref. 2.)

tory muscles are subjected to an excessive mechanical load, leading to a series of changes within the neuromuscular command chain. Part of this change includes a reduction in the central stimulation frequency of the fatigued respiratory muscle. The rate of progression to complete respiratory muscle task failure will depend on the relationship between the supply and demand variables in any single patient. The clinician should focus his or her therapeutic efforts on this relationship. Therapy that reduces the mechanical workload will obviously reduce energy demand. On the supply side, a number of metabolic and nutritional factors influence respiratory muscle capacity and deserve attention.

The reversal of muscle dysfunction by rest distinguishes muscle fatigue from muscle weakness, which is characterized by an inability to achieve a target force under any condition. Muscle weakness results from atrophy of individual myofiber units or biochemical changes within the skeletal muscle in contrast to the metabolic changes of the fatigue state. Muscle fatigue and weakness are not independent parameters of muscle function, however, as respiratory muscle weakness is associated with a reduced work capacity and early fatigue (4). A variety of nutritional factors to be discussed will predispose the COPD subject to both respiratory muscle weakness as well as respiratory muscle fatigue.

## III. Role of Nutritional Status in Patients with Respiratory Disease

### A. Respiratory Muscle Function

Protein-calorie malnutrition (PCM) in the nonstressed animal causes a progressive reduction in body weight and skeletal muscle mass including diaphragm muscle mass (9–11). These changes in animal models of PCM have been confirmed by human autopsy studies (12,13). The loss of muscle protein in PCM appears to preferentially affect specific muscle fibers.

The rat diaphragm muscle is composed of several developmentally regulated myosin heavy chains (MHC), including fibers characterized as slow-(containing predominantly $MHC_{\beta/slow}$) and fast-twitch fibers (containing predominantly $MHC_{2X}$, $MHC_{2B}$, $MHC_{2A}$). Fast-twitch fibers are characterized by a high twitch and tetanic tension, low oxidative and high glycolytic capacity, and a variable resistance to fatigue. In contrast, slow-twitch fibers are characterized by a lower twitch and tetanic tension, high oxidative capacity, and fatigue resistance. In a rat model of protein-calorie deprivation designed to produce a weight loss of approximately 25% of baseline, no significant changes were noted in fiber frequency following PCM. However, this change in body weight was associated with statistically significant reductions in fast twitch diaphragm muscle fiber size primarily of the $MHC_{2X}$ fiber without significant change in slower-twitch fibers (11). These findings confirmed prior work suggesting fast-twitch fiber sensitivity to protein-calorie deprivation in rat and hamster models (9,10). The greater sensitivity of fast-twitch muscle fibers to PCM has also been described in human models of nutritional deprivation (14). Of interest, a similar sensitivity of fast twitch fibers has been demonstrated for the aging process and disuse atrophy (15).

The sensitivity of fast twitch fibers to PCM may relate to circulating or locally produced hormonal factors. Changes in rat diaphragm muscle fibers during PCM are paralleled by changes in circulating insulinlike growth factor (IGF-1) (11). Reductions in the circulating level of this growth factor produce similar atrophy of peripheral skeletal muscle (16,17). Thyroid hormone also plays an important role in the regulation of muscle structure and function, although its exact relationship to specific fiber types is unclear (18). An excess of corticosteroid acts in an analogous fashion to PCM, promoting fast-twitch fiber atrophy (19).

Neuromuscular activity may also play a regulatory role in the determination of fiber composition. Chronic immobilization is noted to affect primarily fast-twitch muscle fibers, and the effects of undernutrition on skeletal muscle are greater in the setting of underactivity (20,21). Additional factors, including blood flow and cellular metabolism, may also serve to regulate fiber dimensions. Although the mechanism is unclear, both human and animal models confirm that fast-twitch fibers appear to be particularly sensitive to PCM.

Biochemical changes within skeletal muscle are also characteristic of PCM. Intracellular electrolytes, including magnesium and phosphate, and intracellular energy stores are abnormal in malnourished COPD patients (22,23). Reductions in phosphate, magnesium, and calcium have been described in COPD patients and can adversely affect respiratory muscle performance, especially in strength parameters (24–26). Abnormal cellular energy metabolism is characteristic of COPD patients with respiratory failure and may relate to nutritional deprivation (27). Biopsies of both intercostal and quadriceps muscles reveal reduced energy stores in the form of ATP and phosphocreatine. The importance of these biochemical changes relative to the muscle atrophy is not firmly established but would be expected to add to the loss of muscle power.

Characteristic neurophysiological changes in muscle are seen with PCM. Physiological studies of isolated muscle strips in both rat and hamster diaphragm have been conducted (9,10). At low stimulation frequencies, isolated muscle strips generate a force of contraction, which represents a small percentage of the maximal tetanic force in contrast to high stimulation frequencies where maximal force is generated. Protein-calorie deprivation results in a reduced force generation primarily at high stimulation frequencies resulting in a shift of the force/frequency curve. Kelsen et al. studied animals over more prolonged intervals (120–180 days) and noted that the tension per unit of muscle cross-sectional area or per unit weight of the animal was similar between undernourished and control animals, suggesting the loss of force results from the associated fiber atrophy (9). In contrast, other investigators have demonstrated that similar physiological changes in diaphragm function occur with acute starvation in as little as 4 days when significant atrophy would be unlikely (28).

Comparison of force generation at low (i.e., 10 Hz) and high (50 Hz) stimulation frequencies in human skeletal muscle shows similar physiological changes (Table 1). The adductor pollicus has been the most frequent site for these types of studies. Loss of force generation at high stimulation frequencies (50 Hz) produces an elevation in the ratio of low- to high-frequency force generation (10:50 ratio) with PCM (23). Additional changes described in these investigations include decreased muscle endurance and prolonged relaxation time. The changes in muscle function are noted to occur without relationship to measurable changes in total body nitrogen (i.e., muscle protein).

The respiratory muscles are not spared from the effects of protein-calorie deprivation. The sternocleidomastoid demonstrates a higher 10:50 stimulus ratio, a slower maximal relaxation rate, and a shorter time to fatigue in malnourished COPD patients compared to normally nourished controls (29). These changes appear to reverse with nutritional therapy over a 3 month interval. Similar changes have been demonstrated for the human diaphragm (29,30).

Human studies in sepsis, surgery, and renal failure suggest that this loss of force at high stimulation frequency may be unique to the malnourished state

**Table 1** Changes in Muscle Physiology with Malnutrition

| Frequency | Stimulation | Parameter | Malnutrition |
|---|---|---|---|
| 10 Hz | Twitch | Strength | Normal |
| 50 Hz | Twitch | Strength | Reduced |
| Supramaximal | Twitch | Relaxation | Prolonged |
| 20 Hz | Repetitive | Endurance | Decreased |

*Source*: Refs. 23, 29.

(31,32). However, this pattern of physiological change is similar to the pattern described for high-frequency respiratory muscle fatigue and can be induced in respiratory muscles during high-intensity exercise, resistive or threshold loading, and sustained hyperventilation (25,33). This raises the possibility of a common etiological mechanism and potential additive effects in the patient with compromised respiratory muscle function.

Malnourished subjects without pulmonary disease demonstrate reductions in respiratory muscle strength and maximum voluntary ventilation (13). Conflicting comparisons between respiratory muscle function and nutritional status have been demonstrated for patients with COPD (34–36). A primary predictor of inspiratory muscle strength is the diaphragm operating length in addition to myopathic processes (36). Therefore, efforts to establish a correlation between nutritional status and inspiratory muscle strength are limited by the ability to control for the multiple variables that affect inspiratory muscle function.

Evidence from the numerous studies of nutritional support in stable COPD suggests that nutritional status may influence respiratory muscle strength. A correlation between positive energy balance (i.e., weight gain) and improvements in muscle strength has been suggested from these studies (37). Those investigations associated with clear weight gain (>2 kg), suggesting positive energy balance, have demonstrated improvements in physiological function. Negative studies (those not associated with improvements in muscle function) have generally not produced significant weight gain in the study population.

In summary, PCM is associated with characteristic changes in skeletal muscle structure and function leading most definitely to reductions in muscle strength. This reduction in strength appears to be sensitive to energy balance and responds to nutritional intervention. What are the implications of these changes for subjects with pulmonary disease? Muscle fibers are recruited for activity based upon the intensity of the stimulus. Those fibers most effected by malnutrition, fast-twitch oxidative fibers, should be used primarily for events that require maximal contractile activity such as coughing. This knowledge suggests that undernutrition may have a minimal impact on basal respiratory muscle activity but a greater role

during activities that require maximal force output. The relative contribution of specific fiber types in the setting of acute respiratory failure is not clear. Patients with high inspiratory impedance (i.e., COPD and ARF) are required to use a greater fraction of maximal output at baseline, suggesting the possibility of a greater reliance on all muscle fiber types. Therefore, malnutrition, with the associated fast-twitch fiber atrophy and reduction in maximal twitch strength, may play a significant role in the pulmonary patient with high respiratory impedance. However, the relationship between the various parameters of muscle function (including strength and endurance) and clinical performance requires further investigation. The relationship between anatomic changes (i.e., atrophy) and physiological changes (muscle weakness) is also not clear, especially during the period of nutritional repletion.

### B. Metabolism and Gas Exchange

Ventilatory demand (minute ventilation $V_E$) varies directly in relation to tissue metabolism (carbon dioxide production, $V_{CO_2}$). Other factors that determine $V_E$ include the deadspace fraction of ventilation ($V_D/_T$), and the blood carbon dioxide level ($P_{CO_2}$) as defined by the equation

$$P_{CO_2} = k\frac{V_{CO_2}}{V_E - (1 - V_D/V_T)} \quad (1)$$

In the absence of disorders associated with hypermetabolism (i.e., fever, hyperthyroidism), the rate of $CO_2$ production is determined by the basal metabolic rate (BMR). Basal metabolic rate is generally determined by the size of the lean tissue mass (38). However, BMR in stable COPD patients does not appear to correlate directly with indicators of lean tissue mass (39). One potential explanation for this variance would be the metabolic activity of the respiratory muscles.

Under normal conditions the energy cost of ventilation comprises a small fraction (1–2%) of total energy requirements. However, measurements in COPD subjects suggest that the energy cost of ventilation may contribute to a greater fraction of resting metabolism (5–10%) (40,41). This may be especially true in the setting of acute respiratory failure.

The metabolic cost of ventilation in respiratory failure can be relieved by mechanical ventilatory support. The cost of weaning from this ventilatory support has been estimated as high as 15–20% of total energy expenditure, again suggesting that a significant fraction of resting metabolism is utilized for respiratory muscle activity (42,43).

Commonly utilized prediction models for estimation of metabolic requirements are based on parameters that attempt to estimate lean tissue mass (38). Variable respiratory muscle energy requirements could result in poor accuracy of these models in predicting caloric requirements for COPD patients. This lack of

validity has been confirmed for the Harris-Benedict equation in COPD subjects (39,44). In contrast, alternative models have been published and may offer improved accuracy (45).

In addition to the potential for respiratory muscle activity to regulate metabolism and therefore ventilatory demand, the provision of nutrient support can play a similar role. The augmentation of metabolism associated with all types of nutrient support is termed diet-induced thermogenesis. The change in $CO_2$ production associated with dietary intake is dependent on the magnitude of caloric intake and the substrate composition.

The basic stoichiometry of fuel oxidation and storage suggests that the composition of caloric intake determines the level of $CO_2$ production. The respiratory quotient (RQ) is a comparison of the rate of carbon dioxide production ($V_{CO_2}$) to oxygen consumption ($V_{O_2}$) for complete oxidation of a given substrate. The value varies with the nature of the substrate and is recognized to be approximately 0.7 for triglycerides, 0.8 for amino acids, and 1.0 for glucose. The greater degree of $CO_2$ production relative to $O_2$ consumption characteristic of carbohydrate administration is used as the argument for selecting various substrates in pulmonary patients. These values assume complete fuel oxidation to $CO_2$ and water and no intermediary metabolism. Caloric intake in excess of metabolic requirements is not oxidized for energy but rather stored for subsequent use. The provision of carbohydrate calories in excess of demand leads to net lipogenesis and storage in this format. Lipogenesis is associated with a respiratory quotient, which can exceed 1.0.

In theory, the respiratory quotients for substrate oxidation suggest that the use of fat as the primary fuel source would result in a lower $CO_2$ production and therefore reduced minute ventilation. This concept has led a number of investigators to advocate a high-fat diet for COPD patients with respiratory failure. However, the benefit of altering the ratio of fat to carbohydrate in pulmonary patients when calories are supplied appropriate to energy demands continues to be debated.

Patients with respiratory failure from a variety of etiologies have been studied regarding this issue (46–50). Comparison between isocaloric pure carbohydrate formulas and formulas with mixed carbohydrate:fat ratios confirms that the mixed formulas generally result in lower $CO_2$ production. The magnitude of the effect is greatest with comparison of the extremes (100% carbohydrate vs. 75% lipid) and with caloric intake in excess of energy demand ($\geq 1.5 \times$ REE). Comparison of variable formula composition after adjustment for appropriate caloric requirements suggests minimal advantage to adjusting carbohydrate:fat ratios (50). To place the issue in perspective, the change in $CO_2$ production associated with changing fat:carbohydrate ratios is less than metabolic changes associated with daily ICU activities (51).

Talpers, in a population of patients with respiratory failure of mixed etiolo-

gies, suggested that carbon dioxide production ($V_{CO_2}$) increased a mean of 15% in subjects fed a caloric intake 1.0 × REE, 33% in subjects fed a caloric intake 1.5 × REE, and 54% in subjects fed 2.0 times the measured REE (50) (Fig. 2). The beneficial effects of nutritional intake must consistently be weighed against this potential stress to the gas exchange process. During periods of unstable gas exchange or tissue oxygenation (i.e., critical illness), the acute administration of large caloric loads is contraindicated. Even in more stable patients, calorie administration in excess of energy requirements may result in excess $CO_2$ production, which can be deleterious.

Examination of Eq. (1) suggests that if the administration of nutrient support produces a 25% increase in $V_{CO_2}$ in a patient with a baseline $V_{CO_2}$ of 200 ml/min and a $V_D/V_T$ of 33%, the required change in minute ventilation for a constant $P_{CO_2}$ will be approximately 1.5 liters. In comparison, if the patient has a $V_D/V_T$ of 66%, the required change in minute ventilation will be approximately 3.1 liters. The impact of nutrient administration is therefore greatest in the presence of a high respiratory drive (low $P_{CO_2}$) and a high deadspace ventilation.

Protein administration has also been proposed to influence the ventilatory demand through alterations in ventilatory chemosensitivity (ventilatory drive). Zwillich et al. suggested that protein administration, following a period of nutritional deprivation, is associated with increased ventilatory responses to hypoxia and hypercapnia (52). Askanazi et al. administered two levels of protein intake (12 and 24 g of $N_2$/day) to six nutritionally depleted patients and suggested a greater effect on ventilatory response in the high-intake population (53). Additional work by these investigators has suggested that branched-chain amino acids may play an important role in mediating the effect of protein on respiratory drive (54,55). Dietary intake of amino acids is postulated to influence central nervous system neurotransmitters through competitive transport of substrate at the blood-brain barrier (56). The magnitude of this effect and the potential role for manipulation of dietary protein intake as a therapeutic tool is not firmly established. Attempts to utilize branched-chain amino acids as a therapeutic tool for respiratory drive in postoperative patients has not been beneficial (57,58). Whether these findings are important to the chronic administration of protein in patients with respiratory disease is unclear.

The intravenous administration of fat emulsions is commonly employed in nutritionally depleted patient populations to prevent essential fatty acid deficiency and provide a source of calories. Studies have reported conflicting results as to whether intravenous lipid administration affects parameters of gas exchange (59–61). The primary adverse effect appears to be a reduction in oxygenation and may be related to the magnitude of the underlying lung disease and rate of lipid administration (61). Intralipid infusion may modulate oxygenation by changing plasma prostaglandin levels (62). Local prostaglandin production is important in the regulation of pulmonary ventilation:perfusion relationships (62). Although

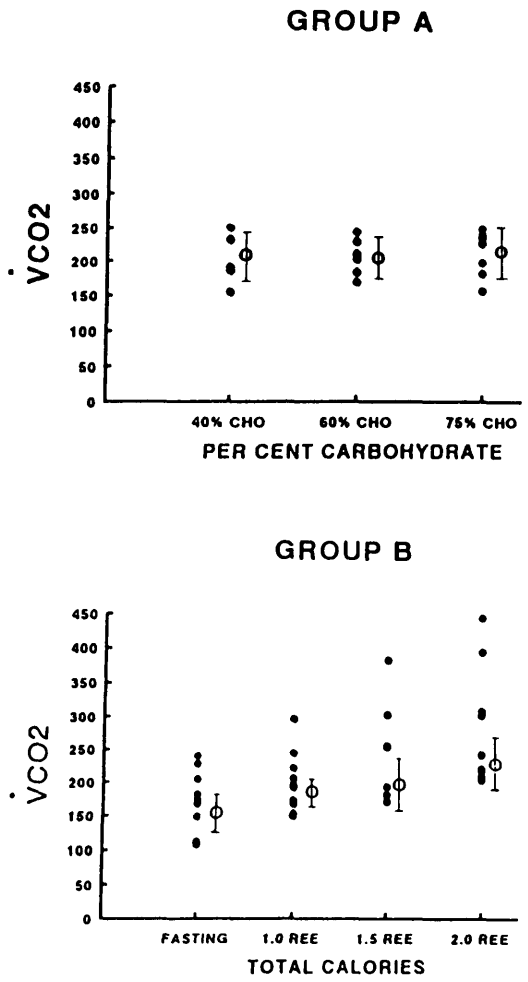


**Figure 2** Comparison of the change in $CO_2$ production between variable rates of isocaloric carbohydrate administration (Group A) and variable rates of calorie administration (Group B). Note the increase in $CO_2$ production seen with increasing rates of calorie administration, which is not seen with isocaloric administration of variable carbohydrate diets. (From Ref. 50.)

evident, the reported changes in gas exchange remain of little apparent clinical significance and can be eliminated with slow infusion rates (4–8 hours). No significant changes have been reported with oral or enteral administration of fat solutions.

In summary, COPD patients with respiratory failure may have a unique relationship between lean tissue mass, respiratory mechanics, and resting metabolism. The potential beneficial effects of nutrient support must be titrated against the metabolic demand this support places on the ventilatory system. While individual substrates have variable effects on metabolism and gas exchange that are defined, the primary focus of nutrition support must be the selection of caloric support appropriately adjusted to energy demands.

### C. Host Defense Mechanisms and Infections

Severe malnutrition adversely affects the immune system (63). Complement activity, humoral immunity, and especially cell-mediated immunity are all altered in malnourished states (64).

The changes in cell-mediated immunity can affect the resistance to pulmonary infection. Clearance of *Listeria* organisms in a rat model of malnutrition and infection was impaired (65). Clearance of organisms less dependent on cell-mediated immunity, such as *Staphylococcus* and *Pseudomonas*, appears to be less affected. The level of protein in the diet, the duration of the diet, and the age of the animal appears to determine the magnitude of the effect PCM has on the immune system (66). Production of cytokine mediators by alveolar macrophages may also be altered in PCM (66). Adherence of gram-negative bacteria to human squamous epithelial and ciliated airway epithelial cells is also increased in animal models (67). This bacterial adherence would favor tracheal and lower airway colonization and presumably contribute to an increased infection risk.

Despite the information gained from the study of animal models, the relationship of PCM to infection risk in adult medical-surgical disorders is less clear. The lack of reliable clinical tools to assess the level of "immunocompetence" in these patients has severely limited progress in this area.

The most common clinical tools used for the immunological assessment of nutritional status are delayed cutaneous hypersensitivity, total lymphocyte counts, and lymphocyte-stimulation assays. Postoperative surgical patients as well as undernourished patients with COPD demonstrate abnormalities in these markers (68–70). However, no single marker of overall immune status has been identified that correlates with an increased susceptibility to infection.

Both the adequacy of protein-calorie support and possibly the nutrient composition of that support can modulate immune function. Extensive animal work has suggested a potential therapeutic role for manipulation of fat source, amino acid content, and nucleotide intake in the regulation of immune function

(70). Human studies, although not specifically conducted in COPD patients, have compared omega-3 to omega-6 fatty acids as a nutrient source and suggested that tests of immune function are improved with a diet rich in omega-3 fatty acids (71). Arginine, an amino acid traditionally considered nonessential, is recognized to stimulate lymphocyte function in laboratory studies and may have similar effects in clinical medicine (72). Further clinical work in human subjects is needed with these substrates before definitive conclusions can be determined.

The route of nutrient administration may play an important role in host defense, especially in patients with critical illness on mechanical ventilation. Either the intravenous or the enteral method of providing nutrient support appears to result in the same nutrient balance (73–75). The enteral method of feeding is generally preferred, as this represents a more physiological route of feeding with a minimized risk potential.

Enteral feedings may have interactions with host defense mechanisms specifically as it relates to the complication of nosocomial pneumonia in critically ill patients. One hypothesis suggests that nosocomial pneumonia results from tracheal colonization and recurrent aspiration. The prime route of tracheal colonization is from gastric reflux of enteric organisms associated with gastric colonization. Gastric acidity appears to play an important role in the prevention of gastric and subsequent tracheal colonization. Although not definitively established, the common practice of stress ulcer prophylaxis that elevates gastric pH in the critical care setting, along with continuous enteral feeding, may predispose to gastric colonization and subsequent bronchopulmonary infections (76).

A second hypothesis holds that nosocomial infections, including pneumonia, result from a translocation of bacteria across the gut lumen. Animal models suggest that burns, sepsis, and parenteral nutrition lead to intestinal atrophy and an increased risk for translocation of enteric organisms into the bloodstream (77). While enteral feeding, with the associated risk of gastric colonization, might favor bacterial translocation, parenteral feeding is associated with gut atrophy (77). Early initiation of enteral feeding may work to maintain the gastrointestinal epithelium and reduce the incidence of bacterial translocation. Randomized trials have suggested that early enteral feeding in postoperative surgical patients results in a significant reduction in nosocomial pneumonia relative to parenteral nutrition (78). The reduction in pneumonia in the enteral feeding population in these studies argues against enteral feeding being a risk factor for pneumonia.

Enteral feeding continues to be the preferred method of nutrient administration whenever possible because of the lower overall risk profile. Nutrient support is believed to be important in the maintenance of immunocompetence and resistance to nosocomial infections. In addition to the provision of protein and calorie support, the interrelationships between nutrient administration, gastric colonization, aspiration, and intestinal lumen translocation require further investigation.

## IV. Approach to the Nutritional Care of the Patient with COPD and Respiratory Failure

### A. Pathogenesis of Nutritional Dysfunction in COPD Patients with Respiratory Failure

The approach to protein-calorie support of the patient with COPD and respiratory failure will be influenced by the underlying disease process. Patients with ARF secondary to pneumonia and/or sepsis may differ from patients with simple exacerbations of COPD in terms of disease pathophysiology, nutrient requirements, and therapeutic goals. Each patient must be considered on an individual basis with recognition of the underlying disease process. However, general principles apply to the nutritional support of all patients who present with respiratory failure.

The change in body mass associated with medical illness is dependent on the balance between synthesis and catabolism. An ongoing process of synthesis and breakdown of body carbohydrate, lipid, and protein stores is present in all patients. When the catabolic rate exceeds tissue anabolism, net loss of lean tissue mass occurs. In clinical disorders, tissue catabolism usually refers to the loss of lean tissue (protein) mass as measured by nitrogen loss in the urine.

The metabolic response to starvation is characterized by hypoglycemia, increased insulin counterregulatory hormones, and depressed insulin secretion (Table 2). Protein synthesis is reduced with a relative decrease in urinary nitrogen excretion. Turnover of body fat stores is increased with ketone body formation (79).

In contrast, the metabolic response to critical illness (e.g., sepsis, trauma,

**Table 2** Comparison of Metabolic Response to Starvation and Critical Illness

| | Starvation | Critical illness |
|---|---|---|
| Metabolism | ↓ | ↑ |
| Protein synthesis | ↓ | ↑ |
| Protein catabolism | = | ↑ |
| Urinary $N_2$ | ↓ | ↑ |
| Lipolysis | ↑ | ↑ |
| Glucose | ↓ | ↑ |
| Insulin | ↓ | ↑ |
| Gluconeogenesis | ↑ | ↑ |
| Glucagon | ↑ | ↑ |
| Ketosis | ↑ | ↓ |

injury) is characterized by hyperglycemia, increased insulin counterregulatory hormones, and increased insulin secretion. The release of substrate-mobilizing hormones include glucocorticoids, catecholamines, and other counterregulatory hormones acts to inhibit the activity of insulin, which normally serves as the primary anabolic hormone for skeletal muscle and adipose tissue. Muscle proteolysis is noted secondary to the effects of these insulin counterregulatory hormones, inflammatory mediators, and/or the requirements of inflammatory cells and sites of tissue injury for amino acids (glutamine) (80). The increased rates of protein catabolism result in an elevated urinary nitrogen excretion. Increased plasma glycerol concentrations suggest a high rate of turnover in endogenous fat stores, although serum free fatty acid concentrations are reduced. An incomplete relationship between free fatty acid concentrations and lipid turnover is recognized (81). Limited fasting ketosis is noted despite the evidence for increased turnover of fat stores.

The magnitude of this stress response is proportional to the stress severity up to a threshold limit and is also influenced by the underlying medical condition. The response, in general, is less with severe preexisting malnutrition.

The accelerated tissue catabolism of critical illness was initially attributed solely to an elevated metabolic rate. In the absence of adequate substrate, tissue catabolism was believed to develop from the body's attempts to meet energy requirements through "autocatabolism." However, in certain conditions the energy requirements of critically ill patients are not markedly in excess of normal requirements despite accelerated nitrogen loss (82). Muscle catabolism provides amino acid release to the liver, which may serve as an adaptive function to allow synthesis of acute phase reactants and proteins for wound healing (83). Net urinary nitrogen excretion is often highly variable depending on the host response to the underlying condition.

In contrast to our knowledge regarding the stress response in critical illness, studies of metabolism in COPD patients with respiratory failure are lacking. Changes in the hormonal milieu and intermediary metabolism for COPD patients with respiratory failure are believed to mirror changes in the critically ill patient, although possibly to a lesser magnitude. The role of medications especially corticosteroids and theophylline, in intermediary metabolism, is unknown.

Some insight can be gained from work done with noncritically ill COPD patients, however. Evidence to date suggests that the primary disorder for COPD patients is an imbalance in energy demands. Unlike the severely stressed critically ill patient, urinary nitrogen loss is modest and net nitrogen retention is achieved with caloric administration adjusted to meet energy requirements (75). Insulin resistance is not characteristic of the stable COPD patient during nutritional repletion.

Provision of nutrient support to the COPD patient with respiratory failure must occur at the appropriate time period. As nutrition support involves a metabolic (and often volume) stress to the patient, it should generally not be initiated in

the face of marked hemodynamic or gas exchange instability. During periods of prolonged stress, efforts are directed to preserve the present nutritional state as the hormonal milieu previously described is unfavorable for tissue anabolism. Restoration of body cell mass is delayed until a more favorable clinical status exists to support net nitrogen retention.

### B. Nutritional Assessment of the Patient with Respiratory Disease

The initial step in the nutritional evaluation of the COPD patient with respiratory failure is an assessment of preexisting nutritional status and theoretical nutritional risk using a variety of assessment tools. The goals for the nutritional assessment include (1) identification of patients at increased risk for an adverse outcome who might benefit from nutritional support and (2) evaluation of the response to nutritional intervention. The clinician is faced with a wide range of tests utilized in an effort to address these issues. However, no single parameter provides adequate sensitivity and specificity with the broad range of respiratory illness to make it alone useful for nutritional assessment. In fact, some investigators suggest that nutritional assessment tools offer no particular advantage over a careful clinical examination (84). The use of nutritional assessment tools in COPD patients with respiratory failure has not been extensively investigated. The majority of studies have been conducted in outpatients. General principles and available information will be reviewed. More detailed reviews of this topic in patients with pulmonary disease are published elsewhere (37).

The nutritional assessment of the respiratory patient should begin with a detailed history and physical examination. Although weight loss is accepted as a "normal" finding in acute respiratory failure and the terminal phases of severe chronic obstructive lung disease, the diagnosis of weight loss secondary to pulmonary disease is best approached as a "diagnosis by exclusion." A careful search for factors that might contribute to weight loss independent of the patient's lung function such as occult malignancy, malabsorption syndromes, hyperthyroidism, alcohol abuse, or cardiac disease is indicated.

Nutritional assessment parameters can be divided into those parameters that measure the size of body compartments and those that attempt a functional assessment. The simplest most accessible and risk-free parameter utilized for nutritional assessment is body weight. In the absence of major shifts in total body water, weight loss over a prolonged time interval is a marker of negative energy balance. If possible, a weight history to include usual weight and any history of recent weight loss should be utilized. A nonvoluntary weight loss of greater than 10% is considered evidence for significant PCM (85). The monitoring of body weight in the critical care setting is significantly limited, however, by marked shifts in extracellular water.

Anthropometry involves the application of simple measurements of skinfolds, circumferences, and skeletal breadths to divide the human form into fat, muscle tissue, and skeletal mass. The techniques of measurement have been standardized, although their application to the critically ill patient population has not been extensively documented. Anthropometric measurements have limited utility in the acute setting as a monitoring tool as they are insensitive to the short-term effects of nutritional support.

The body compartment of most interest to investigators studying malnourished COPD patients with respiratory failure would be total body muscle mass. Unfortunately, no simple, accurate measure of muscle mass is available. The use of 24-hour creatinine excretion as an index of muscle mass is based on the knowledge that creatinine is contained almost totally within skeletal and smooth muscle and is converted at a constant rate by a nonenzymatic reaction to creatinine, and that creatinine, once formed, is excreted exclusively by the kidney at a fixed rate (86). Unfortunately, the use of urinary creatinine as a measure of muscle mass is not without error. Factors that influence creatinine excretion include age, diet, exercise, stress, and renal disease, making the reliable use of this parameter in critically ill patients difficult. The monitoring of the amino acid 3-methylhistidine (3-MH) in the urine as an index of muscle mass is limited by similar problems.

Numerous additional tests are described that attempt to divide body composition into its component portions. Separation of fat from lean body mass (the majority of which is muscle tissue) can be achieved with the use of densitometry (by underwater weighing), isotope techniques, electrical impedance, or radiographic imaging. The majority of these techniques expose the patient to radiation risk or are too costly and/or impractical for use in the acute critical care setting.

Bioelectric impedance is appealing for use in all malnourished populations, including COPD patients, due to its simplicity, safety, low cost, and repeatability. This technique measures the body's impedance to a low-level (800 μA) 50 kHz current. The fat-free mass, which contains electrolytes, behaves like an electrical conductor and influences the measurement. Four surface electrodes are placed on the unilateral hand and foot. Recent work by Schols et al. has suggested that this technique can more accurately estimate lean tissue mass in COPD subjects than traditional measurements (87). This technique may offer advantages over body weight assessment in selecting stable COPD patients with reduced lean body mass who might benefit from nutritional intervention (88). However, the technique assumes a constant relationship between total body water and lean tissue mass. This assumption is likely to be invalid in the critically ill COPD patient with respiratory failure secondary to edema formation.

In addition to assessment of somatic protein stores, visceral protein stores are evaluated most commonly through determination of plasma proteins. Visceral proteins synthesized by the liver include albumin, transferrin, retinol-binding protein, and prealbumin. Total hepatic protein synthesis declines during fasting,

and, therefore, the plasma levels of these proteins should provide an effective marker of nutritional status. The rate of decline in the plasma level is proportional to the rate of turnover. Those proteins with a shorter plasma turnover will be more sensitive to acute changes in nutritional status. Albumin has a relatively slow turnover relative to retinol-binding protein or prealbumin and therefore provides a more optimal index of chronic nutritional depletion. However, the level of these proteins is influenced by numerous factors, including liver function and volume status, and the values must therefore be interpreted with some element of caution.

These proteins have also been used to assess the response to a nutritional intervention. Prealbumin and retinal-binding protein have been suggested as more appropriate markers of the effectiveness of short-term nutritional intervention typical of the COPD patient with respiratory failure due to their shorter half-life (89). However, their accuracy in this setting is not clear.

The weight, anthropometric, and biochemical assessments of body compartments can be supplemented by a functional-based assessment. Assessment of immune function can be employed utilizing common skin recall antigens (e.g., mumps, *Candida*, streptokinase-streptodornase). The lack of 10-mm induration at the intradermal injection site is characteristic of anergy. Multiple factors in addition to malnutrition, however, can influence the results and limit the use of this parameter.

Alternatively, parameters of muscle function can be used as a component of the nutritional assessment. As previously discussed, muscle strength is reduced in PCM and characteristically responds to nutritional support. While more complex tests of neurophysiological function including force-frequency curves are physiologically more precise, the technical expertise required limits their widespread acceptance. In contrast, voluntary tests of maximal muscle strength, such as hand-grip dynamometry or respiratory muscle pressures, are readily available and familiar to most respiratory care practitioners.

Hand-grip dynamometry is a widely applicable test that has been shown to predict postoperative complications and may be more sensitive to postoperative risk than other standard nutritional parameters such as weight loss, TSF, AMC, or plasma proteins (90,91). Hand-grip strength is reduced in malnourished stable COPD patients and improves with nutritional support adequate to produce weight gain (29,92).

Respiratory muscle strength is generally assessed by measurement of maximal mouth or transdiaphragmatic pressures generated against an occluded airway. Kelly et al. demonstrated a 33% increase in respiratory muscle strength following 2 weeks of parenteral nutrition in hospitalized ventilator dependent patients (93). As previously discussed, nutritional support in stable patients with chronic airflow obstruction is likewise associated with improvements in respiratory muscle strength.

The application of the numerous tools described for nutritional assessment

to the COPD patient with acute respiratory failure is often limited. Practical issues dictate that a weight history and careful physical examination, possibly supplemented by biochemical assessment of visceral protein stores, be utilized to select patients at high nutritional risk. In a similar fashion, measurement of body weight, visceral proteins, and preferably functional status including muscle strength can be used to monitor the response to a nutritional intervention.

### C. Determination of Energy and Protein Requirements

Energy requirements for the patient with respiratory failure can be determined using simple prediction models or, alternatively, assessed through the technique of indirect calorimetry (Table 3). Total daily energy expenditure includes the basal metabolic rate, the energy expenditure of thermogenesis, and the energy expenditure of activity. The Harris-Benedict (HB) equation is most commonly utilized to estimate the basal metabolic rate (BMR).

In critically ill patients, the HB-predicted BMR can be adjusted for energy requirements of activity (a factor of $1.2 \times$ BMR is commonly used for hospitalized patients). In addition, a modification for the severity of the illness is introduced using stress factors. A common stress factor for the COPD patient with ARF is 12.–1.5. A wide individual variation between estimated values and measured energy expenditure is recognized. Measured energy expenditures are generally greater than basal (uncorrected) HB values but less than HB values corrected for stress and activity factors (94).

Alternatively, total energy requirements can be predicted using more simpler estimates, which incorporate only the degree of stress and body weight (95). For the COPD patient with respiratory failure, an estimate of approximately 30 kcal/kg of body weight appears to be adequate. A model which employs only weight has been developed for COPD patients with acute respiratory failure based upon similar principles (45).

Indirect calorimetry utilizes the gas exchange measurement of oxygen consumption ($V_{O_2}$) and carbon dioxide production ($V_{CO_2}$) to predict energy expenditure (EE). Although often viewed as the "gold standard" in estimating energy expenditure, the technique is not without limitations. These include significant day-to-day measurement variability, unreliability at high inspired oxygen concentrations (i.e., $>0.50\ F_iO_2$), the need for technical expertise, and the assumption of a steady-state metabolic relationship (i.e., no fever) and ventilation. Additionally, an unclear relationship between intermittent metabolic measurements and total daily energy expenditure in ICU patients is recognized (51).

None of the approaches to estimating caloric requirements appears to be particularly advantageous. Understanding the metabolic response characteristic of the underlying disease process will best assist the clinician in correct estimation of caloric needs.

**Table 3** Methods for Estimation of Metabolic Requirements in COPD Patients

(1) Harris-Benedict Equation (BMR)

male BMR (kcal/24 hr) = 66.5 + 13.7 × weight (kg) + 5.0 × height (cm) − 6.78 × age (yr)

female BMR (kcal/24 hr) = 655.0 + 9.56 × weight (kg) + 1.85 × height (cm) − 4.68 age (yr)

stress factors

| | |
|---|---|
| starvation | 0.7–0.9 × BMR |
| elective surgery | 1.2–1.3 |
| injury | 1.1–1.3 |
| sepsis | 1.3–1.6 |
| burn | 1.5–2.1 |
| fever | 1.1–1.2 × BMR/°C above 37.8 |

Calculated RMR (resting metabolic rate) = BMR × activity factor (1.2) × stress factor

(2) Prediction based upon body weight and degree of stress

| | |
|---|---|
| minimal stress | 20–30 kcal/kg/24 hr |
| moderate stress | 30–40 kcal/kg/24 hr |
| sepsis/trauma | 40–50 kcal/kg/24 hr |
| severe burn | up to 80 kcal/kg/24 hr |

(3) Prediction based upon COPD specific equation

males [11.5 × weight (kg)] + 952

females [14.1 × weight (kg)] + 515

(4) Prediction based upon indirect calorimetry

EE (kcal/24 hr) = 3.586 $V_{O_2}$ (liters/day) + 1.443 $V_{CO_2}$ (liters/day) − 21.5

Protein requirements of COPD patients with acute respiratory failure are usually within the 1–1.5 g/kg body weight per day range. Protein infusion rates of ≥2 g/kg/day have been reported to produce greater nitrogen balance in critically ill patients, although the advantages and potential risks of this approach are not generally accepted. An energy-to-nitrogen ratio in the range of 150 kcal:g is an appropriate goal for the majority of patients. Although branched-chain amino acids may improve nitrogen retention in the critically ill patient, the significance of this effect continues to be debated such that this approach is not uniformly practiced. The adequacy of protein intake can be assessed through determination of 24-hour urinary $N_2$ excretion and calculation of nitrogen balance. Similar to metabolic measurements, this parameter is best assessed after the patient has reached a steady state with respect to disease activity and dietary intake. The difference between nitrogen intake (calculated as the dietary protein intake in g/6.25) and nitrogen excretion provides an estimate of total body nitrogen conservation. Urinary urea nitrogen represents 80–90% of total urinary nitrogen.

Nonprotein calories are most frequently provided as a mixture of carbohydrate and lipid calories. While the optimal nonprotein calorie mix for critically ill patients with respiratory failure continues to be debated, a few general guidelines are accepted.

The use of glucose as the sole source of nonprotein calories is no longer advised. Glucose supplementation results in incomplete suppression of gluconeogenesis and fat oxidation despite excess carbohydrate administration. A minimum supply of 150 g/day of glucose is needed for glucose-dependent tissues (e.g., CNS). The maximum glucose oxidation rate in critically ill patients is 4–6 mg/kg/min, which suggests the maximum glucose supply per day should be 3–5 g/kg (96). The use of an isolated glucose energy source for parenteral nutrition can suppress fatty acid release and promote a fatty acid deficiency syndrome (97). Complications resulting from excessive carbohydrate administration are recognized and include hyperglycemia, hyperosmolar syndrome, and hepatic steatosis. Mixed lipid and carbohydrate administration produces equivalent nitrogen sparing to glucose administration alone (75,97,98).

The most common lipid sources for both enteral and parenteral nutrition consists of fatty acids (FA) of the omega-6 type. For parenteral support the most common lipid emulsions consist of long-chain triglycerides (LCT). Complications related to lipid administration are seen primarily in patients receiving parenteral therapy and include hypoxemia and immunosuppression. As previously mentioned, the risk of hypoxemia increases with faster rates of administration and appears to be mediated through altered local prostaglandin production. Immune suppression may occur in relation to the type of fatty acid used in both parenteral and enteral nutrition, although the clinical significance of this is currently being investigated.

Nonprotein calories provided in a 50:50 ratio of carbohydrate to fat are well tolerated. This ratio can have significant variability without adverse consequences.

Is nutrient support beneficial to the emaciated COPD patient with respiratory failure? While strong basic science and clinical evidence as outlined supports the provision of nutrient support to these patients, a randomized trial of nutrient support for this clinical indication has not been published. Small uncontrolled observations support the practice, and no randomized, controlled trial will likely be possible in the future (99,100). In the absence of this confirmation, the "potential" beneficial effects of nutrition support must be continuously weighed against the very real risk of complications.

Obesity (>20% over ideal body weight) is also frequently seen in the COPD patient presenting with respiratory failure. Data from 153 stable patients in a Veterans Administration pulmonary clinic revealed a high incidence (37.2%) of obesity (>120% midpoint of the Metropolitan tables) (101). In this obese

population, two thirds maintained or gained weight in the year prior to the evaluation.

The effect of obesity on respiratory function has not generated the same degree of attention as undernutrition and COPD. It is logical that metabolically inactive, added fat mass increases the work for the compromised respiratory system, particularly during weight-bearing activities. Therefore, one could assume that reductions in body fat mass would be beneficial to this patient population.

Obesity is notoriously resistant to treatment, and current recommendations for treatment are comprehensive in scope, including careful assessment and long-term, multidisciplinary intervention. Little insight is available in published studies regarding the optimal management of the obese COPD patient with respiratory failure. While it is tempting to restrict caloric intake in these patients, calorie deprivation in the obese subject is recognized to adversely affect neuromuscular function (23). Further research in this category of patient is indicated before definitive recommendations are possible.

### D. Selection of Feeding Methodology and Formula

Enteral or oral feeding is the favored method of nutrient administration for all COPD patients with respiratory failure as it is nutritionally and metabolically equivalent to parenteral feeding, maintains gut morphology and function, provides stress ulcer prophylaxis, and avoids the risk of a vascular catheter. This last factor is especially important, as a pneumothorax resulting from central venous access for parenteral nutrition can have disastrous consequences in a COPD patient.

It should be emphasized that, whenever possible, COPD patients should consume a regular diet and not be subjected to specialized feeding formulas. Even patients on mechanical ventilation can maintain adequate nutrient support via simple oral intake under the right conditions. However, for a significant percentage of patients a specialized feeding formula will be required.

The formulas for enteral nutrition can be grouped into categories including polymeric, oligomeric (elemental), or modular formulations (102). For the vast majority of COPD patients with normal gastrointestinal function, a simple polymeric formula will be sufficient. Polymeric formulas are isotonic to hypertonic formulas containing carbohydrate, fat, and protein (intact or partially hydrolyzed). They provide an appropriate level of vitamins and minerals when infused at the correct infusion rate for caloric support. Most solutions are lactose free and palatable for oral intake.

As a general rule, small-bore feeding tubes and a continuous infusion should be utilized. The rate of administration is gradually advanced. There is no clear indication to dilute feedings especially with isoosmolar feeds and normal GI function.

### E. Complications of Nutritional Support

A full discussion of the complications of nutritional support is beyond the scope of this review. A focus on the complications of enteral nutritional support will be emphasized, as parenteral support should be required only in the rare COPD patient.

As a general rule, the incidence of metabolic complications is less with enteral nutrition compared to parenteral nutrition, yet they still occur. The refeeding of patients with longstanding malnutrition has been associated with a characteristic pattern of metabolic change described as the "refeeding syndrome" (103). The classic electrolyte deficiency is hypophosphatemia, but hypomagnesemia, hypocalcemia, and hypokalemia are also recognized. Cardiac failure has been described in the early refeeding period with this syndrome.

Hyperglycemia is common in the critically ill patient with nutritional support secondary to persistent gluconeogenesis, lack of tissue insulin sensitivity, incomplete glucose oxidation, and elevated insulin counterregulatory hormones. This problem can be addressed through a reduction in total caloric intake, a reduction in the carbohydrate:fat ratio of the nonprotein energy source, and, if necessary, the use of supplemental insulin. Large doses of supplemental insulin, however, only act to increase cellular uptake without increasing glucose oxidation at the risk of worsening insulin resistance.

Enteral feeding complications can also include mechanical complications related to the access device. These include tube occlusion, epistaxis and nasopharyngeal erosions, sinusitis, esophageal reflux, and pneumothorax during placement (104). Gastrointestinal complications including nausea and vomiting occur in 10–20% of patients and are dependent on the volume and rate of infusion, presence of lactose intolerance, and presence of delayed gastric emptying. Diarrhea during the administration of enteral feeding is also common and has been associated with greater volumes and rate of infusion, bacterial contamination of the infusion, drug-induced disease (antibiotics, antacids, quinidine, $H_2$ antagonists), and hypoalbuminemia.

Finally, the risk of aspiration pneumonia has received much attention. While placement of a nasoduodenal tube is often advocated to minimize this complication, nasoduodenal tube location appears to be necessary only for patients at high risk for complications secondary to gastric retention, e.g., gastroparesis, reflux, pancreatitis, etc. The risk of aspiration can be minimized most significantly by maintaining the patient at a 45° angle during the feeding interval.

## V. Summary

The respiratory system and metabolism are tightly linked by the requirement for oxygen as a fuel source for substrate metabolism and the need to excrete the

metabolic waste product of carbon dioxide. As a result, nutrient support places a demand on the respiratory system. The performance of the respiratory system is influenced by the nutritional status of the patient. Neuromuscular function is impaired in the setting of protein-calorie malnutrition, and resistance to infection may be impaired.

Our knowledge in the field of nutrition support remains in its infancy. While we have learned the "how" of providing calorie and protein support to our patients, our knowledge regarding the "why" and "what type" remains most incomplete. This is especially true for the COPD patient with acute respiratory failure.

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# 20

# Chest X-Ray in the Chronic Obstructive Pulmonary Disease Patient with Acute Respiratory Failure in the Intensive Care Unit

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## I. Introduction

Radiographic abnormalities are common findings in acute exacerbation of chronic obstructive pulmonary disease (COPD). Chest radiography is the least invasive and most accessible examination for the initial evaluation of the precipitating factors reviewed elsewhere in this book and for the monitoring of these acutely ill patients. However, there is disagreement about the need for routine chest radiography in this setting. In a retrospective analysis, Sherman et al. were the first to assess the diagnostic value of chest radiographs in a population of patients admitted for exacerbation of COPD (1). In that study, the authors found that all clinically significant radiographic abnormalities were identified by a history of congestive heart failure, coronary artery disease, edema, chest pain, or a white blood cell count of more than 15,000/ml along with a polymorphonuclear leukocyte count of more that 8,000/ml. They concluded that the use of high-yield criteria could eliminate unnecessary studies while assuring recognition of important new radiographic abnormalities. However, Emerman and Cydulka observed that almost one fourth of the radiographic abnormalities were not predictable on the basis of these selective criteria in a population having an emergency department discharge diagnosis of exacerbation of COPD (2). Routine chest radiography

should be considered in these patients to diagnose treatable, radiographically apparent abnormalities. Furthermore, careful daily monitoring of all invasive life support elements seen on the radiograph is one of the first tasks to accomplish when interpreting intensive care unit (ICU) chest radiographs (3).

## II. Technical Considerations

Approximately 6–37% of portable chest radiographs taken in the ICU are technically suboptimal (4,5). Improving the quality of imaging data in the ICU requires that the team of technicians be well trained and convinced of how important their role is in patient management. With the help of the nursing staff, all of the lines, catheters, tubing, wires, and the hose of the ventilator, whenever possible, should temporarily be held away from the chest wall included in the radiograph. Technicians should be instructed to take the chest film at full inspiration or at the peak inspiratory cycle of the ventilator for patients receiving mechanical ventilation. Optimally, all of the necessary information to read the film correctly should appear on adhesive labels attached to each ICU film. These include the degree of erectness, the angulation of the x-ray beam, the tube-to-film distance, the milliamperage and kilovoltage, the mode of ventilation, and both peak pressure and positive end-expiratory pressure. Moreover, these details enable the technical conditions of the technique to be reproduced and, consequently, proper assessment of changes in mediastinal or cardiac diameters (6). Technical parameters and positioning are not standardized. Most institutions use high kilovoltage (120–130 kV), short exposure times, and fast film-screen combinations to obtain optimal examinations. The supine position has been found to be the most reproducible in critically ill patients. On an erect posteroanterior view, the mean width of the systemic vessels extending from the thoracic inlet to the heart is 48±5 mm. The supine vascular pedicle width is increased an average of 20% without appreciable change between anteroposterior and posteroanterior views (7,8). Based on 20 subjects, Harris reported a 49% increase in the width of the superior mediastinum from a posteroanterior upright deep inspiration radiograph to an anteroposterior supine end-expiration film (9). Because of the spatial constraints in the ICU room, the tube-to-film distance is 40–48 inches, as opposed to the conventional 72 inches; therefore, there is an increase of approximately 5% in the vascular pedicle width. Similarly, the anteroposterior technique results in an approximately 15–20% magnification of the heart (10). The reduction of focus-to-film distance accounts for 10–15% of the observed magnification. Provided that the radiologists and the ICU clinicians are aware of the factors that can affect assessment of vascular pedicle and heart width, the size and change of size in serial radiographs can be of considerable clinical value (6).

## III. Infection

The most common precipitant of acute respiratory failure is airway infection (11,12). As in pulmonary edema, the patterns of pneumonia are bizarre in patients with emphysema. The morphological destruction of the lung produced by emphysema, i.e., a sparse capillary bed, absence of pores of Kohn, and distorted bronchiolar architecture, explain the disorganized pattern of consolidation (13). The dilated air spaces are rarely filled and the exudate is confined to the normal areas of lung that surround the emphysematous foci (14,15). Occasionally the inflammatory process outlining the emphysematous areas produces an appearance that may simulate extensive cavitary lung disease or honeycomb lung (Figs. 1,2) (16). Moreover, steroids may dramatically change the appearance and course of an inflammatory process in the lung (17). Thus, the radiologist must be aware of the treatment regimen and clinical picture of the patient to correctly interpret the radiograph (18). The differential diagnosis obtained from a unilateral or atypical pattern of edema may be difficult. More than the "gravitational shift test" employed by Zimmerman et al. (19), the visualization of changes typical of interstitial edema and a trial of diuretics in such equivocal patients are often very revealing (6,20). Infection of a bulla is usually manifested on an erect chest x-ray by a fluid level within the air sac, with or without some degree of consolidation in the surrounding parenchyma. The fluid level disappears on the supine chest radiograph, and additional views could be useful. The differential diagnosis of fluid within a bulla includes hemorrhage, which occasionally can be so massive as to require emergency surgery (21).

## IV. Hemodynamic Alterations

One must maintain a very high index of suspicion for left-heart failure in patients with COPD when reading films, since it may be very difficult to detect and is more frequent than in patients with normal lungs (22–24). Chest radiography is the most commonly used noninvasive technique for assessing pulmonary edema in critically ill patients. Several authors have demonstrated a correlation between radiographic findings and quantitative measures of lung water content (25–27). Milne et al. have shown that erect chest radiography is very accurate in distinguishing among three vascular patterns: normal, pulmonary plethora, and redistribution from left-sided congestive heart failure (28). In their study, the three most discriminating radiographic criteria were the distribution of pulmonary edema, the distribution of pulmonary blood flow, and the width of the vascular pedicle. A kappa analysis, which is an accepted measurement of agreement among observers, indicates that the performance of experienced radiologists in identify-

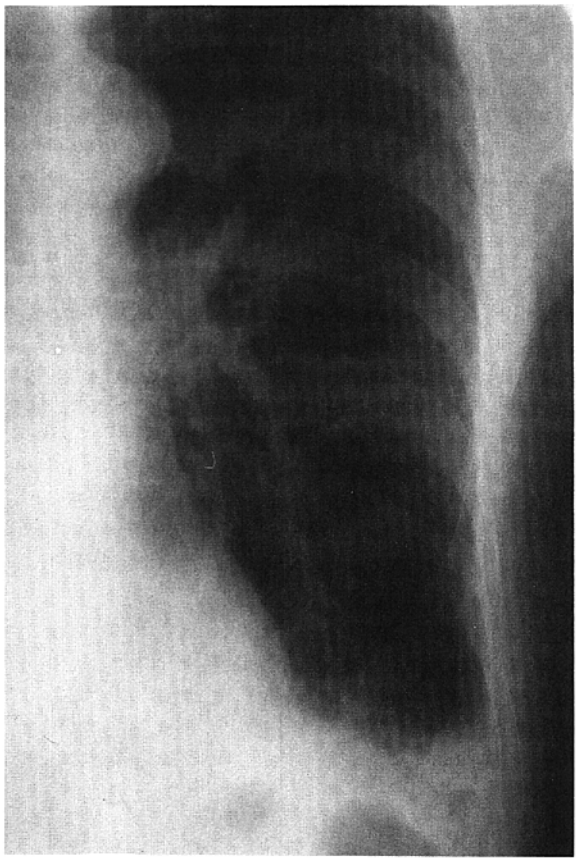

**Figure 1** Anteroposterior radiograph showing incomplete consolidation of emphysematous left lower lobe by pneumonia.

ing signs of chronic heart failure and grading its severity is sufficiently high for clinical use (29). Further reports outline the limitations of the chest radiograph for determining the cause of pulmonary edema, particularly in the presence of cardiogenic pulmonary edema in the ICU patient (29–31). In 61 patients with cardiac failure, 60% of the cases showed a vascular-pedicle width greater than 53 mm and 40% were in the normal range (28). Among 45 patients with severe pulmonary edema, 87% of patients with hydrostatic edema but only 60% of patients with increased permeability edema were correctly identified using the criteria mentioned above (30). Hermann et al. found that, in patients with an elevated left

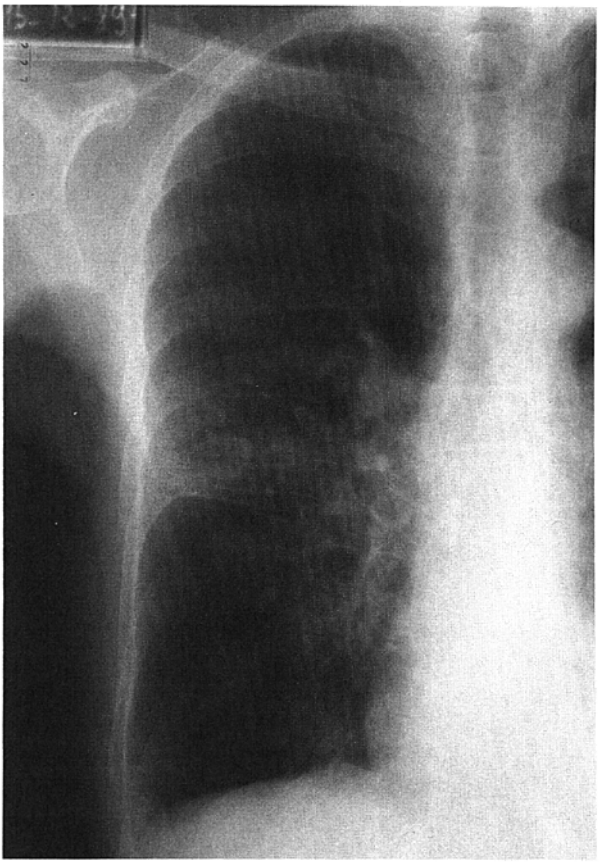

**Figure 2** Posteroanterior roentgenogram of the chest showing severe bronchiectasis with superimposed pneumonia.

ventricular end diastolic pressure over 20 mmHg, 38% showed no radiological signs of chronic heart failure (29). Ravin has suggested that changes in the diameter of the end-on anterior segmental arteries of the upper lobes compared with the accompanying end-on anterior segmental bronchi may be useful in the diagnosis of chronic heart failure (32,33). The diagnostic value of an altered artery-bronchus ratio in common abnormal pulmonary flow states was recently assessed in the following groups of subjects: erect healthy subjects, erect subjects with pulmonary vascular plethora, erect subjects with clinical evidence of decompensated left-sided congestive heart failure, supine normal subjects, and supine

subjects with clinical evidence of decompensated congestive heart failure (34). The supine radiograph was found to be equal to the erect chest radiograph in helping distinguish between normal and abnormal vascularity. But none of the subjects in these previous studies had a history of preexisting pulmonary disease. It is well known that preexisting lung diseases, such as emphysema, can dramatically alter pulmonary vascularity and compromise the ability to correctly determine vascular patterns with radiographs (29).

In patients with chronic bronchitis, the vessel margins are already blurred and peribronchial cuffing can be seen, which can preclude a satisfactory assessment of the artery-bronchus ratio. The superimposed changes of edema will therefore be impossible to detect unless there is a recent radiograph available for comparison (6). In a similar manner, the nonuniform character of the capillary-bed destruction in emphysema causes an unusual "patchy" distribution of pulmonary edema (16,35) (Fig. 3). At times, upper, lower, or unilateral predominance of the superimposed edema occurs and the criteria mentioned above cannot be used (36). Further evaluation is still needed.

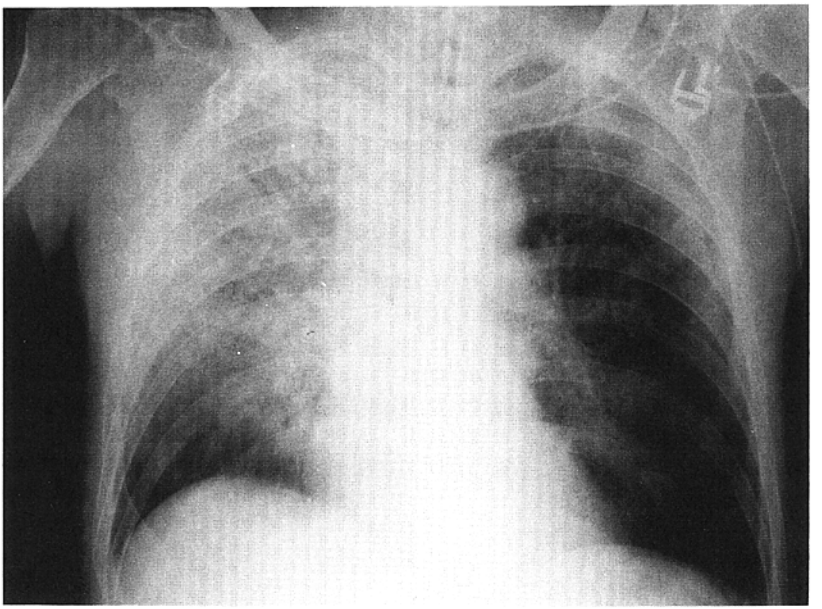

**Figure 3** A chest radiograph of a 62-year-old male with advanced emphysema, showing a right upper-lobe consolidation with "honeycomb" appearance.

## V. Pulmonary Embolism

Pulmonary embolism has been found at postmortem examination in 28–51% of patients with emphysema (37,38). The diagnosis of pulmonary embolism in patients with significant COPD may be particularly difficult, thus the frequency with which nonfatal decompensation occurs as a result of pulmonary embolism is unknown (39,40). The diagnosis of pulmonary embolism depends largely on roentgenographic imaging techniques, because symptoms, signs, and laboratory tests are insensitive and nonspecific. Numerous investigators have described radiographic abnormalities seen in association with pulmonary embolism (41–45) including oligemia, polyemia of the unobstructed lung, dilated hilar arteries, elevated hemidiaphragm, dilated pulmonary artery trunk, pleural effusion, atelectasis, and infiltrate. While several studies found that the diagnosis of pulmonary embolism may be established by interpretation of the chest radiograph alone, others have reported that plain film findings alone do not allow a reliable diagnosis to be made. In a recent study, the chest radiographs of 1063 patients with suspected pulmonary embolism obtained from the multicenter Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial were analyzed (46). Because of the low prevalence of the Westermark sign (11.2%), the positive and negative predictive values were unreliable in determining which patients had pulmonary embolism. In that study, oligemia was a chest radiographic finding highly specific (92%) for the prediction of pulmonary embolism at angiography. However, the specificity of this sign in COPD is doubtful, since regional oligemia is regarded by several investigators as the most reliable roentgenological sign of emphysema (20,47,48). The prevalence of the Fleischner sign (prominent central artery) was not significantly different in patients with pulmonary embolism compared with patients in whom this diagnosis was excluded. This sign cannot be used in COPD patients who exhibit evidence of pulmonary hypertension. In fact, in a PIOPED trial subset of 108 COPD patients, no roentgenographic abnormalities occurred with significantly greater frequency among patients with pulmonary embolism than among those without pulmonary embolism (49). However, no previous chest radiographs were available for comparison in these studies. These criteria should be reevaluated concomitantly with the serial radiographs undoubtedly available in such patients to detect subtle changes in the size of pulmonary arteries or the extent of oligemia. In addition, it should be kept in mind that one of the most valuable aids in the diagnosis of pulmonary emboli, ventilation-perfusion lung scintigraphy, becomes relatively insensitive in the presence of COPD. Pulmonary angiography remains the gold standard for embolus diagnosis (50,51). Furthermore, spiral volumetric computed tomography can reliably depict thromboemboli in second-to-fourth-division pulmonary vessels, thereby avoiding the risks of catheterization in patients with severe pulmonary hypertension (52).

## VI. Pneumothorax

Although the diagnosis of pneumothorax can be difficult in patients without prior pulmonary disease, it presents an even more challenging problem in the patient with COPD. No one symptom seems to clearly distinguish the patient with pneumothorax from the many patients with acute respiratory failure due to other causes. The roentgenographic appearance of pneumothorax in these ICU patients is governed by the anatomy of the pleural recesses and the effects of gravity and lung compliance on the displacement of pleural air (53,54). In the supine or semierect position, subpulmonary pneumothoraces are especially cryptic and can be fatal (55). The lack of retractility prevents total collapse of the underlying lung, and the margins of the collapsed lung may be difficult or impossible to detect. Comparison with previous radiographs can demonstrate a smooth hemidiaphragm with loss of its scalloped appearance and visualization of the inferior surface of a diseased lower lobe. A poorly outlined hyperlucent upper quadrant of the abdomen associated with visualization of the superior surface of the diaphragm may be the only clue present (56). The anterior costophrenic sulcus can be seen (57). Other signs of subpulmonary pneumothorax include an unusually distinct cardiac apex and pericardial fat (58). In anteromedial pneumothorax, recognition of the left superior intercostal vein and the superior pulmonary veins on the left or right side may be the only sign. Classic signs include a sharp visualization of the superior vena cava, azygos vein, supra-diaphragmatic inferior vena cava and right paratracheal line on the right and of the left subclavian artery over the apex of the left lung. A cross-table lateral view, which is not easy to perform in critically ill patients, or a unilateral 45° oblique view could help to demonstrate anterior and anterobasal pneumothorax, respectively (59). The conventional radiographic diagnosis of apicolateral pneumothorax depends upon the recognition of a thin white line representing the visceral pleura outlined by intrapleural air. However, many ICU patients have parenchymal disease with lack of compliance, which prevents collapse and visualization of the line. Furthermore, regional differences in compliance can explain the visibility of more severely involved segments of the lung beyond the pneumothorax. Films taken during expiration may aid in identifying the pneumothorax (60). Pneumothorax commonly occurs in association with small bullae of the lung apices and rarely with large bullae involving the lower lobes (20). Although the rate of enlargement of bullae is not predictable, in the majority of cases they become progressively larger. It can be extremely difficult if not impossible to distinguish between a huge bulla and a large pneumothorax. The collapsed lung surrounding such bulla can improve the visibility of the abnormal air collection in the bulla.

A pneumothorax is considered to be under tension when the pressure in the pleural space equals atmospheric pressure. The presence of air-trapping, dimin-

ished compliance, and mechanical ventilation may prevent tracheal shift to the opposite side in the presence of tension (61). Moreover, a further decrease in the motion of the involved side may not be evident because diaphragm excursions are already restricted. Additional findings in tension pneumothorax may be a flattening of the heart border and other vascular structures including the superior and inferior vena cavae.

## VII. Iatrogenic Complications in the ICU

The incidence of abnormal radiographic findings is reported to be between 43 and 70% in intensive care units (5,62,63). Iatrogenic thoracic complications account for 5–10% of hospital deaths. In a prospective analysis of 1354 x-ray films from 167 patients, Bekemeyer et al. found 34.5% new abnormalities or a malpositioned tube or catheter (64). Changes in the diagnostic approach or therapeutic measures, excluding catheter position adjustments, occurred after 28.5% of the examinations. Hall et al. discovered 17.6% new major findings using only chest radiography (65). These data support the use of daily chest radiographs in critically ill patients.

### A. Endotracheal Tubes

The postintubation radiograph is obtained to confirm the proper positioning of the tip of the endotracheal tube and to rule out complications. Ideally, the tube tip should be 5±2 cm from the carina when the head and neck are in the neutral position, or at least 3 cm below the vocal cords, which lie over C5 or C6 in most adults. Conrardy et al. (66) demonstrated that, during neck flexion assessed by the visualization of the chin at the top of the radiograph, the tube descends toward the carina (range 0.2–2.3 cm), whereas during neck extension assessed by visualization of most of the cervical spine, the tube rises (range 0.2–5.2 cm). Thus, any adjustments of the tube need to take into account the flexion of the neck on the radiograph. On a bedside radiograph, the carina overlies T5 through T7 in 92% of the patients. Therefore, even when the carina is not readily identified, it can be considered that a tube tip positioned at the level of T3 or T4 is safe (67,68). Approximately 10–15% of endotracheal intubations result in complications, with intrusion into the right main bronchus being the most common (69). The lack of ventilation of the left lung and even the right upper lobe if the tube is in the bronchus intermedius causes the collapse of these lobes. Rarely, overexpansion of the right lung results in pneumothorax. Distension of the tracheal lumen by the inflated balloon cuff indicates an overdistension that should be corrected. Insertion of an endotracheal tube into the esophagus is an infrequent but life-threatening complication of endotracheal intubation. Smith et al. have reviewed

radiographic findings, including projection of the tube lateral to the trachea, gastric distension, esophageal air, and deviation of the trachea by the balloon (70). The location of endotracheal tubes can be identified accurately in 92% of films made with the patient in a right posterior oblique position with the head turned to the right to prevent superimposition of the trachea and esophagus. A less common but more serious complication of endotracheal intubation is tracheal rupture. Previously reported findings include pneumothorax, pneumomediastinum, subcutaneous emphysema, and respiratory distress, all of which can occur in the absence of tracheal rupture (71–73). Early recognition is necessary to decrease morbidity and mortality. The presence of an endotracheal tube with its distal portion oriented to the right with a distended balloon, a reduced distance from high volume-low pressure balloon to the tip of the endotracheal tube with or without pneumomediastinum, should prompt further investigation of the airway with either CT or bronchoscopy (74). However, an overdistended balloon does not always indicate tracheal rupture. It may be seen in chronically intubated patient or in preintubation tracheal enlargement, but also in the COPD patient (74).

### B. Central Venous Catheters

Prospective studies have shown that approximately one third of central venous pressure catheters will be incorrectly positioned at the time of initial evaluation (75,76). Catheters should be positioned parallel to the long axis of the superior vena cava with the tip at the level of the azygos vein. The position of the tip of the catheter must be monitored daily to avoid catheter perforation (Fig. 4). This complication seems to arise in approximately 0.4–1.0% of catheter placements (77,78). Clinical features compatible with central-line erosion include new or progressive cardiopulmonary symptoms, increased pleural effusions, mediastinal widening, and increasing central venous pressure combined with progressive systematic hypotension. Free blood return does not exclude the diagnosis. The tip of the catheter positioned against the wall of the vessel and a sharply curved catheter have been described as signs of impending vessel perforation (79).

### C. Pulmonary Artery Catheters

The ideal position of the Swan-Ganz pulmonary artery catheter is within the right or left main pulmonary artery (80). If the catheter tip is more than 2 cm lateral to the hilum, it is too peripheral (Fig. 5a) (68). Perforation of a pulmonary artery by a balloon-tipped flow-directed Swan-Ganz catheter is a rare but serious complication, with an estimated frequency of about 0.2% (81). Percutaneous transcatheter embolization of the lacerated pulmonary artery or pseudoaneurysm has been successful in several cases (82,83). Intracardiac redundancy may lead to arrhythmias (Fig. 5b) (84).

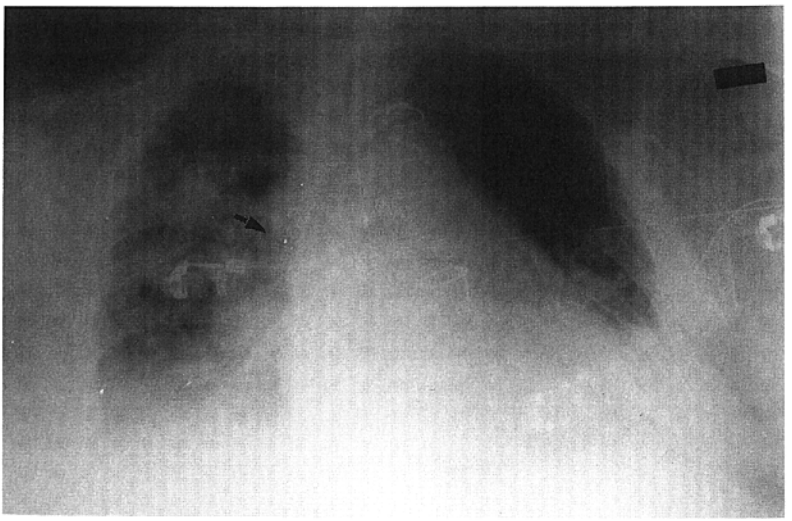

**Figure 4** A left-sided catheter is positioned with its tips (arrow) in the "danger zone" of the proximal superior vena cava at a 45° angle to the vessel wall.

### D. Feeding Tubes

Inadvertent tracheobronchial placement of narrow-bore feeding tubes may result in significant patient morbidity. Pleuropulmonary complications include the following: pneumomediastinum, subcutaneous emphysema, pneumothorax, pneumonitis, pulmonary hemorrhage, pleural effusions, empyema, bronchopleural fistula, hemothorax, and perforation of the esophagus (85–89). Complications occur in 0–7.6% of the patients (90–92). Auscultation of the left upper quadrant of the abdomen can be misleading. Therefore, it is crucial to obtain immediate postintubation radiographs of the chest and abdomen to confirm satisfactory positioning of the feeding tubes prior to administration of liquid nutrients (Fig. 6).

### E. Chest Tubes

The optimal position of a chest tube differs with the substance being drained from the pleural space. In pneumothorax, because the air moves preferentially to the less dependent zones, the tube should ideally be inserted into the third intercostal space at the level of the anterior axillary line. Conversely, in pleural effusion, the optimal position is posteroinferior in the eighth intercostal space at the level of or slightly posterior to the middle axillary line (93). If inserted properly, the catheter's side holes should be within the pleural space. Moreover, the nonopaque wall

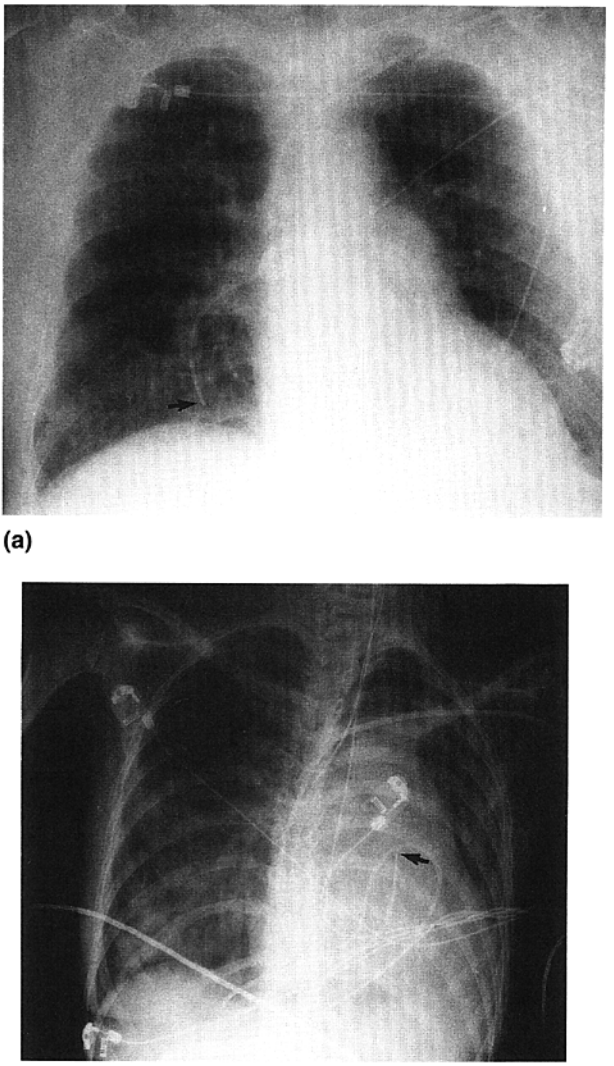

**Figure 5** Positioning of the Swan-Ganz pulmonary artery catheter. (a) Anteroposterior radiograph showing a malpositioned catheter with its tips directed towards the base of the right lower lobe (arrow). (b) Anteroposterior film demonstrate an excessive looping of the catheter in the right atrium and right ventricle. Note the position of the catheter tip (arrow).

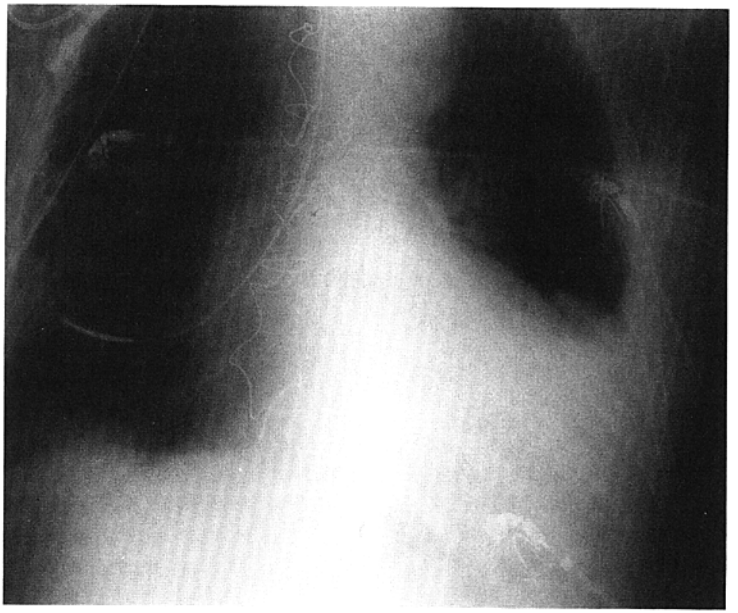

**Figure 6** Anteroposterior radiograph of the chest showing an inadvertent malposition of a nasogastric tube into the airways of the right lower lobe.

is visible over a pneumothorax because there is air both inside and outside the tube. An extrapleural location must be suspected when the outer edge of a chest tube is invisible and the tube lies adjacent to aerated lung or pneumothorax. Additional oblique radiographs are necessary to confirm improper placement. In the case of pleural effusion, consolidated lung, or subcutaneous placement, the invisibility of the outer edge of the tube is insignificant (94). The chest radiograph should rule out the following complications: inadequate drainage, empyema formation, bleeding from a tear of an intercostal artery, unilateral pulmonary edema following rapid removal of a large effusion or pneumothorax and entrapment of the lung (68,93). The radiographic demonstration of a pulmonary density in the region of the side or end hole of the chest tube should alert the radiologist to the possibility of the latter (95).

## VIII. Summary

This review has focused on the impact of the chest radiograph on the diagnosis of the factors precipitating chronic respiratory failure and on the iatrogenic compli-

cations in the ICU. Preexisting lung diseases, such as COPD, greatly modify the findings that are attributed to the presence of infection, hemodynamic alterations, pulmonary embolism, and pneumothorax. Little information is available, and further prospective studies are required to evaluate the sensitivity and specificity of chest radiographic findings in such patients. Likewise, because computed tomography provides an accurate assessment of the patterns and distributions of lung diseases, it should enable confident diagnosis in patients with nonspecific radiographic findings. The main value of the chest radiograph is to diagnose treatable, radiographically apparent abnormalities, to exclude diagnoses that clinically mimic pulmonary embolism and to aid in the interpretation of the ventilation-perfusion scintiscan. Finally, the radiologist must assure accurate and timely detection of complications associated with the use of endotracheal tubes, Swan-Ganz catheters, central venous catheters, and feeding and chest tubes.

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# 21

# Prognosis of Acute Respiratory Failure in Patients with Chronic Obstructive Pulmonary Disease

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## I. Introduction

Acute respiratory failure (ARF) is a frequent and severe complication in patients with chronic obstructive pulmonary disease (COPD). ARF, manifested by hypercapnia, and respiratory acidosis, or arterial hypoxemia, is a common cause of death in COPD patients. ARF is often precipitated by conditions such as respiratory infection, ventricular dysfunction, pulmonary embolism, and surgery. Consequently, ARF is often cited as a reason for admission to intensive care units (ICUs) (1,2).

As the prevalence of COPD has increased over the last 25 years (3,4), the care of patients with ARF associated with COPD has become a major medical, social, and economic issue. Although the immediate rates of recovery and survival to hospital discharge in patients with ARF are about 70–90%, with some patients regaining their previous baseline respiratory function, approximately 20–60% of patients require mechanical ventilation during their hospitalization to overcome the acute episode of severe respiratory dysfunction. Mechanical ventilation after intubation exposes COPD patients to potentially severe complications, such as pneumothorax, barotrauma, tracheal injury, nosocomial infections, as well as ventilator dependency (2,5). Furthermore, a certain proportion of these patients

go on to require prolonged ventilation or to become ventilator dependent (6–10). The care of these patients is a major expense in the acute hospital setting and thus is a significant medical and economic problem (11,12). The long-term prognosis after ARF associated with COPD is unfavorable; most studies have reported survival rates of 50–70% one year after an acute episode of respiratory failure and 10–30% after 5 years (8,13–18). Physician estimates of potential patient outcome for ARF with COPD have varied considerably (19). Much of this variability can be attributed to difficulty in empirically weighing the impact of physiological abnormalities, age, and comorbid condition on outcome and in defining patient population for survival estimates.

Improved methods of predicting survival for patients with COPD suffering from an acute episode of respiratory failure is of particular importance to the clinician faced with prolonged, costly, and difficult management of these critically ill patients. Such prognostic information may help guide decision making and promote active or prolonged intervention in COPD patients suffering from ARF. This chapter therefore details the current state of the art for prediction of short-term hospital outcome for patients with ARF as a consequence of COPD.

## II. Prediction of Outcome of Patients with ARF Associated with COPD

The prediction of survival among patients with ARF associated with COPD has received increasing attention in last decade. Recent studies have attempted to describe factors that predict short- and long-term survival in these patients early during the course of an acute episode of ARF (5,10,20–24). However, the prognostic factors chosen for analysis and modeling used to predict outcome have varied considerably.

ARF in COPD patients is associated with a broad spectrum of physiological abnormalities in multiple organ systems. Disturbances in circulation, in renal, neurological, and metabolic function, in the acid-base and electrolyte system, and in nutritional balance are often manifested in ARF. These conditions have an additional and variable confounding effect on patient outcome in addition to the risk of adverse outcomes engendered by the acute respiratory dysfunction alone. Table 1 summarizes the factors that have been found to be associated with short-term outcome in COPD patients suffering from ARF in previous studies. These factors include the nature of the underlying pulmonary disease (e.g., bronchitis or emphysema), physiological reserve (e.g., age, chronic diseases and ability to perform activity of daily life), severity of illness manifested by physiological derangements, complications, and therapeutic response.

The impairment of pulmonary function has been the primary consideration as a risk factor for survival in previous studies. Early parameters of blood gas

**Table 1** Factors Influencing Short-term Prognosis from ARF in Patients with COPD

| |
|---|
| Nature of disease |
| Physiological reserve |
| age |
| comorbidities (cor pulmonale, congestive heart failure) |
| ability to perform activities of daily living |
| Number of previous episodes of ARF |
| Severity of physiological derangements |
| low $FEV_1$, $FEV_1$:FVC ratio |
| high $Paco_2$ |
| acidosis/$[H^+]$ |
| hyponatremia |
| fever |
| low albumin |
| hypotension |
| tachycardia |
| uremia |
| high creatinine |
| hyperleukocytosis |
| coma |
| Complications |
| ventricular failure |
| arrhythmias |
| nosocomial infection |
| hemorrhage |
| renal failure |
| Therapeutic response: vital capacity restitution curve[a] |

[a]Vital capacity restitution curve (VCRC) is a daily measurements of vital capacity curve, showing degree of restitution of pulmonary ventilation function (25).

exchange were found to be of weak value in patients for whom an acute episode of ARF occurred in the presence of long-term respiratory insufficiency (10,18,26). However, in studies by Warren and Jeffrey, initial acidosis (defined as pH $< 7.27$ or arterial $[H^+]$ of at least 55 nmol/liter) was associated with markedly higher mortality rates in patients on controlled oxygen therapy. The physiology of this increase in mortality remains to be explained (16,21). Spirometry measurements such as forced expired volume in one second ($FEV_1$) have been found to be of prognostic value and are considered to be a reliable predictor of respiratory decompensation in patients with COPD in several outcome studies (5,10,14). However, spirometry is not always available at the time of admission to an ICU

and is impossible to carry out in patients with respiratory encephalopathy or coma. It has also been found that $FEV_1$/height squared is not related to mortality in men older than 70 years (27).

Chronological age has been found to be an important prognostic indicator of hospital outcome in many studies (10,14–16,21,22). There is a relationship between advancing age and declining pulmonary function and physiological reserve. A recent study of 3050 elderly patients (age $\geq$ 50 yr) admitted to ICUs has shown that age is an important prognostic factor for prediction of in-hospital mortality among older patients admitted to an ICU with COPD and other diseases of the lower respiratory tract, after controlling for severity of illness (28). This study also reported that age alone was not sufficient to predict outcome of elderly ICU patients, since other factors, such as the primary diagnosis, presence of comorbid conditions, and severity of acute illness, also play a key role in predicting mortality.

Because the response to therapy in such patients is difficult to predict, the clinical management of these patients is often prolonged and frustrating. Therefore, patient response to therapy has been studied as a prognostic factor in some studies. Sluiter et al. (7) reported on a subgroup of patients who failed conservative treatment and subsequently were mechanically ventilated. These patients had a higher mortality rate compared to patients who responded to conservative management and patients who were intubated on arrival at the ICU (78% vs. 13% and 13%). Twenty years after Sluiter's paper, interest has turned to noninvasive mechanical ventilation, which appears to select out an increasing number of patients who respond favorably to this treatment, avoiding the increased morbidity and mortality secondary to undue intubation (29). Tempe et al. (25) reported on the prognostic value of a longitudinal vital capacity restitution curve (VCRC) from daily measurements of vital capacity, showing that after an initial period of increase in the degree of restitution, a more favorable prognosis can be made after 4 days of observation as compared to those whose pulmonary function was not restored as well. But these studies were limited by great variation in clinical management of such patients.

It has been noted by several authors that most hospital deaths in COPD patients are due to subsequent nonrespiratory events such as nosocomial infections, pulmonary emboli, GI bleeding, and ventricular and renal failure (6,7,10, 22). Hanson et al. (20) found that complications on day 5 of intensive care were very important in classifying patients as survivors or nonsurvivors. These complications were associated with a relatively longer ICU stay or mechanical ventilation and greatly increased the risk of death, and they confounded the prediction of patient survival (5,20,30).

However, none of the above-mentioned risk factors were consistently associated with outcome across studies. For example, cor pulmonale or chronic heart failure as complications of COPD were associated with poor outcome in many

previous studies (5,22) but not in others (10,23). The variability in patient population and differences in the case definitions of ARF and its underlying causes, patient exclusion criteria, treatment location and intervention, end-point definition, and sample size might also contribute to the variability in the predicted risk factors. Because of this heterogeneity across prior studies, it is not unexpected that prediction of outcome based on selected subgroups of patients does not represent the entire dimension of this clinical entity and has had only limited success. Kaelin et al. (10) failed to predict 6-month survival using fever, the ratio between $FEV_1$ and forced vital capacity (FVC), age, hyperleukocytosis, $PaCO_2$, number of previous intubations, low-flow oxygen treatment, and plasma protein level as predictors in a group of COPD patients requiring mechanical ventilation for ARF, with an overall correct classification rate of 78%. However, this analysis was limited to 35 patients, in whom some important clinical data such as mental status and shock were not recorded, and in this small group of patients, almost all deaths were due to presence of severe nonpulmonary organ system dysfunction. Another predictive model for 1-year survival, based on activities of daily life, $FEV_1$, albumin level, presence of cor pulmonale, and history of left ventricular failure, was developed in 95 patients (5). This study did not provide a statistical validation for the prediction model. The most recent and the largest study of COPD, which included 322 patients, 45% of whom had COPD as the primary etiology of ARF, found few identifiable prognostic factors associated with immediate survival at time of admission to an ICU (23). The prognostic factors identified in this study included presence of cachexia, low sodium, low systolic blood pressure, high urea, high phosphate, whether the patient was previously confined to the home, initial coma, and requirement of mechanical ventilation in the first 24 hours. There were no differences found in age, underlying diseases, precipitating cause of ARF, the presence of concomitant risk factors, or presence of mechanical ventilation between survivors and nonsurvivors.

Previous literature gives many reasons to believe that it is difficult to predict a given patient's outcome unless adequately detailed information is collected. Furthermore, it is difficult and sometimes inappropriate to apply a predictive model generated from a selected subgroup of patients to forecast outcome in a heterogeneous population.

## III. Prediction and Prognosis Data from APACHE III Study

Our current understanding of short-term probability of survival suggests that mortality from an acute illness is related to the nature of the patient's disease, severity of disease, physiological reserve, and patient's response to therapy (31). Short-term prognosis of acute respiratory failure in patients with COPD can be

predicted by incorporating these factors into an algorithm that is dependent primarily on the severity of overall acute physiology disturbances associated with ARF. To accomplish this prediction of short-term survival, patients with ARF associated with COPD were selected from the APACHE (Acute Physiology, Age, and Chronic Health Evaluation) III Database (32), which comprises 17,440 consecutive patient admissions to 42 ICUs in 40 U.S. hospitals.

## A. Methods

### *Patient Selection Criteria*

A diagnosis of COPD was based on clinical findings on admission or ICD-9-codes 490–492 and 496 as documented in the discharge summary. ARF was defined as a $Pao_2 < 60$ mmHg or $Pco_2 > 50$ mmHg and pH less than 7.35. Most patients were admitted to the ICU with ARF precipitated by conditions such as pneumonia, sepsis, major surgery, with COPD as an underlying chronic disease. A smaller group of patients in the sample had ARF as an acute exacerbation of COPD, with no other cause found.

### *Data Collection*

Patient demographic data, such as age, gender, comorbidities, activities of daily life, admission sources, and primary reasons for ICU admission, were abstracted on ICU admission. Detailed physiological measures and therapeutic intervention measured by Therapeutic Intervention Scoring System (TISS) (33) were collected daily for the first 7 days of intensive care to monitor response to treatment and therapeutic decisions. Activities of daily living were recorded as an index of performance in bathing, dressing, toileting, transferring, continence, and feeding (34). All patients were followed up for time and location of death until hospital discharge. Survival was defined as discharge from the hospital alive.

### *Analysis and Prediction of Outcome*

The APACHE III Score results from the addition of relative weights for the worst value of physiological measurements, patient's age, and chronic health (Fig. 1). A logistic regression equation from 17,440 ICU patients in the APACHE III Database was independently developed and cross-validated. This equation combined the predictive power of the APACHE III Score with major disease category and patient's location prior to ICU admission, allowing a calculation of hospital death risk ($P_{APACHE\ III}$) (32,35).

## B. Results

COPD was a common health problem in the critically ill adult patients in this population, totaling 3236 patients, or 18.6% of the total ICU admissions in the

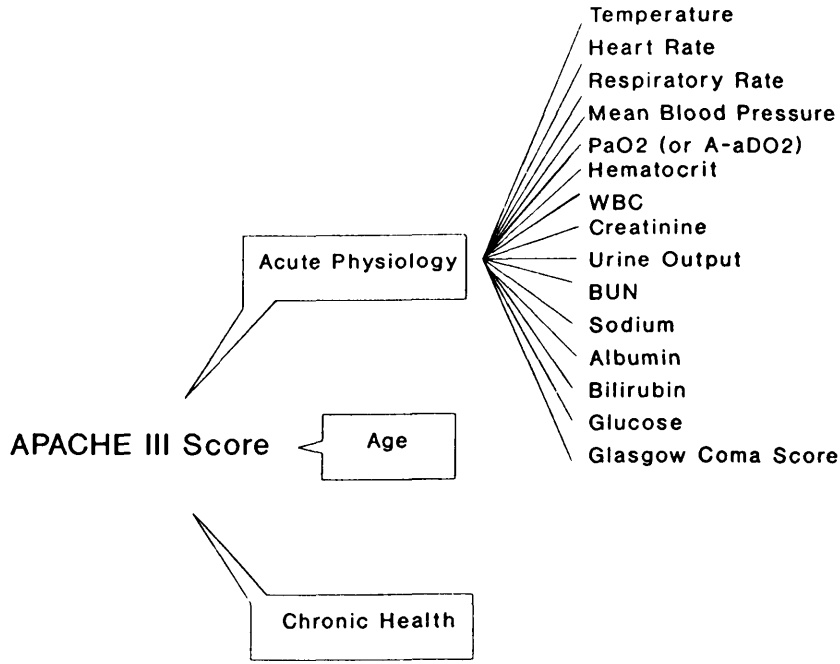


**Figure 1** APACHE III score results from the addition of the estimated weights for the worst value of physiological measurements, patient's age and chronic health. (From Ref. 32.)

APACHE III Database admitted to ICUs with either primary diagnosis of exacerbation of COPD or with other operative or nonoperative diagnoses and with COPD as an underlying chronic disease (Fig. 2). A total of 733 patients were identified with ARF associated with COPD, 62% were male, with a mean age of 67 (± 11) years. Eighty percent had a nonoperative admission diagnosis. Causes of ARF included acute exacerbation of COPD, pneumonia/sepsis, congestive heart failure, pulmonary embolus, respiratory arrest other respiratory diseases, and major surgery (Fig. 3).

Fifty-one percent of the patients required mechanical ventilation during the first 24 hours after admission to the ICU, and 55% were intubated during the first 7 days of intensive care, more in postoperative than in nonoperative patients (68% vs. 52%, $p < 0.001$), with a mean intubation duration of 7.5 (± 14.3) days. One hundred and thirty-three patients required ventilation of 7 days or more. The mean length of ICU stay was 7.1 (± 11.6) days, with an ICU mortality rate of 18.6% and an overall hospital mortality rate of 32.7%.

All COPD Patients in APACHE III Database (N=3236, 18.6%)

With ICU Admission Diagnosis of COPD (11%)

Chronic COPD with Non-Operative ICU Admission Diagnosis (51%)

- CHF (15%)
- Cardiac Arrest (5%)
- Other Cardiovascular Disease (14%)
- Pneumonia (13%)
- Sepsis (6%)
- Pulmonary Embolus (2%)
- GI Bleeding (7%)
- Drug Overdose (2%)
- Diabetes (0.5%)
- Neurologic Diseases (8%)
- Others (27%)

Chronic COPD with Post-operative ICU Admission Diagnosis (38%)

- Cardiovascular (42%)
- Gastrointestinal (26%)
- Respiratory Thoracic (18%)
- Neurologic (6%)
- Others (8%)

**Figure 2** Primary admission diagnosis in 3236 COPD patients in the APACHE III study.

The factors associated with hospital death are shown in Table 2. The survivors were significantly younger (mean age 65 vs. 70 yr, $p < 0.01$), had a higher activities of daily living index, mean arterial blood pressure, serum albumin, and plasma sodium, better mental status as measured by GCS, and lower base deficit, creatinine, BUN, white blood count, and blood glucose levels. There was a statistically significant difference in the first-ICU-day APACHE III Score between survivors and nonsurvivors—58 vs. 94 ($p < 0.001$). The first-day APACHE III Score was normally distributed in a wide range (Fig. 4). Hospital mortality rates of the sample were positively associated with increasing overall physiological derangement as measured by APACHE III Score (Fig. 5).

Hospital mortality rates by age and Acute Physiology (APS III) Score at the time of admission from the APACHE III Study are shown in Figure 6. Hospital

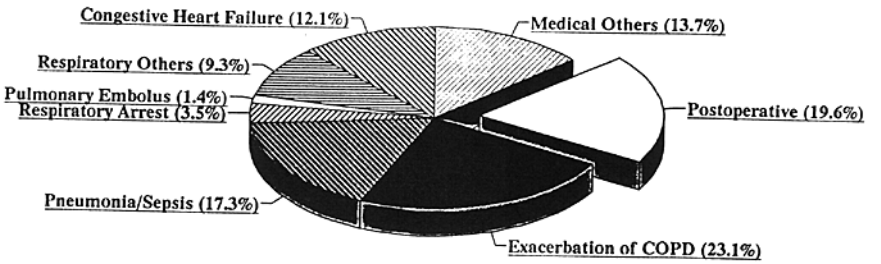


**Figure 3** Precipitating factors in 733 COPD patients who developed ARF.

**Table 2** Factors Associated with Hospital Survival in 733 Patients with COPD Suffering from ARF

| | Survivors (N = 493, 67%) | Nonsurvivors (N = 240, 33%) |
|---|---|---|
| Mean age (yr) | 65 ± 11 | 71 ± 11** |
| ADL Index[a] > D (%) | 8 | 15** |
| Admitted from emergency room (%) | 44 | 30** |
| Mechanical ventilation during first 24 hr (%) | 42 | 70** |
| Mean arterial blood pressure (mmHg) | 91 ± 33 | 69 ± 37* |
| Heart rate (beats/min) | 117 ± 30 | 125 ± 35** |
| pH | 7.34 ± 0.10 | 7.32 ± 0.13* |
| Base deficit (mEq/liter) | −0.12 ± 4.8 | 2.88 ± 7.5** |
| Albumin (g/dl) | 3.4 ± 0.44 | 3.2 ± 0.63** |
| Plasma sodium (mEq/liter) | 137.7 ± 6.2 | 136.1 ± 7.6** |
| Creatinine (mg/dl) | 1.33 ± 1.5 | 1.77 ± 1.3* |
| SBUN (mg/dl) | 21.1 ± 19.4 | 34.6 ± 25.0** |
| Urine output (ml/24 hr) | 2225 ± 1547 | 1599 ± 1450** |
| WBC (1000/mm$^3$) | 13.6 ± 7.2 | 16.6 ± 9.4** |
| Plasma glucose (mg/dl) | 174.0 ± 83.8 | 200.0 ± 126.6* |
| GCS[b] | 13.7 ± 2.8 | 11.2 ± 4.6** |
| First-ICU-day APACHE III score | 58 ± 22 | 94 ± 32** |

[a]ADL Index: Index of Activity of Daily Life.
[b]GCS: Glasgow Coma Scale.
*$p < 0.05$; **$p < 0.01$ between the survivors and nonsurvivors.

mortality rates increased with age after controlling for the severity of illness using the APS III score with logistic regression (chi-square = 29.3, df = 3, $p < 0.001$).

In a chi-square analysis, mortality rates were significantly different among six patient groups who had different precipitating factors of ARF: acute exacerbation of COPD (N = 169, 23.1%), pneumonia/sepsis (N = 127, 17.3%), other respiratory diseases (N = 104, 14.2%), CHF (N = 89, 12.1%), other nonrespiratory medical diseases (N = 100, 13.7%), and postoperative (N = 144, 19.6%) ($p < 0.0001$). Disease group, modeled with APS III and age in a logistic regression equation, had no significant impact on outcome. Figure 7 shows hospital mortality rates after adjustment for severity in two subgroups of patients. Patients with sepsis or pneumonia as a precipitating factor had significantly higher overall mortality than postoperative patients (44% vs. 26%, $p < 0.001$) and higher mortality at each level of APS III.

The 60% of patients transferred to ICUs from other hospital wards had a mean hospital stay prior to ICU admission of 9.1 (± 29) days. Compared with patients admitted from emergency departments, transferred patients had signifi-

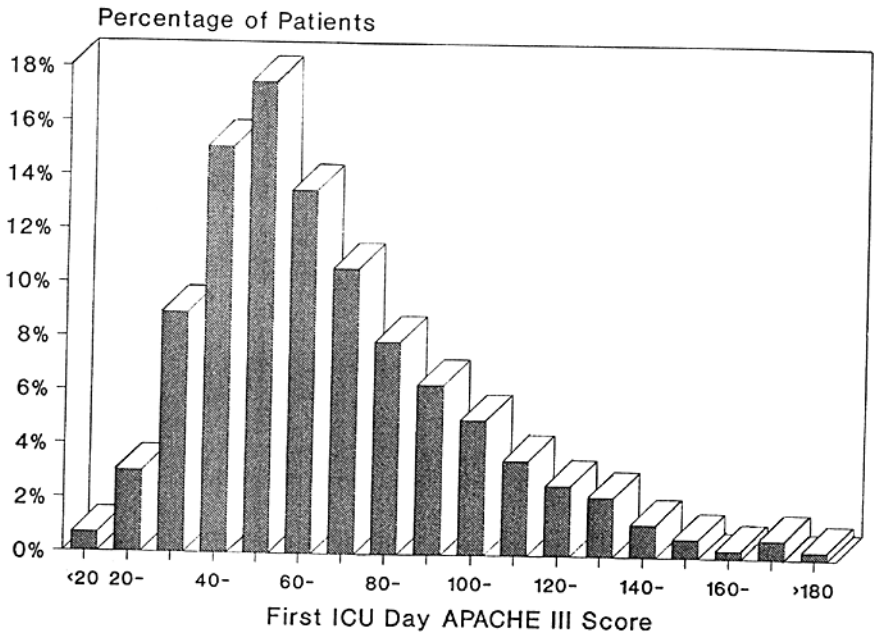


**Figure 4** The distribution of first-day APACHE III score in 733 COPD admissions with ARF.

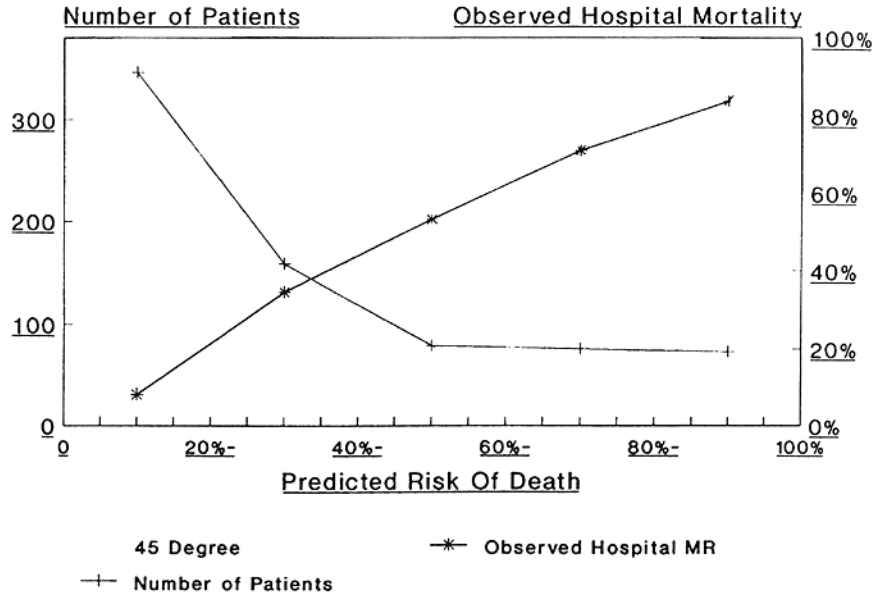


**Figure 5** Predicted versus observed hospital mortality rates in 733 patients with acute respiratory failure associated with COPD from the APACHE III study.

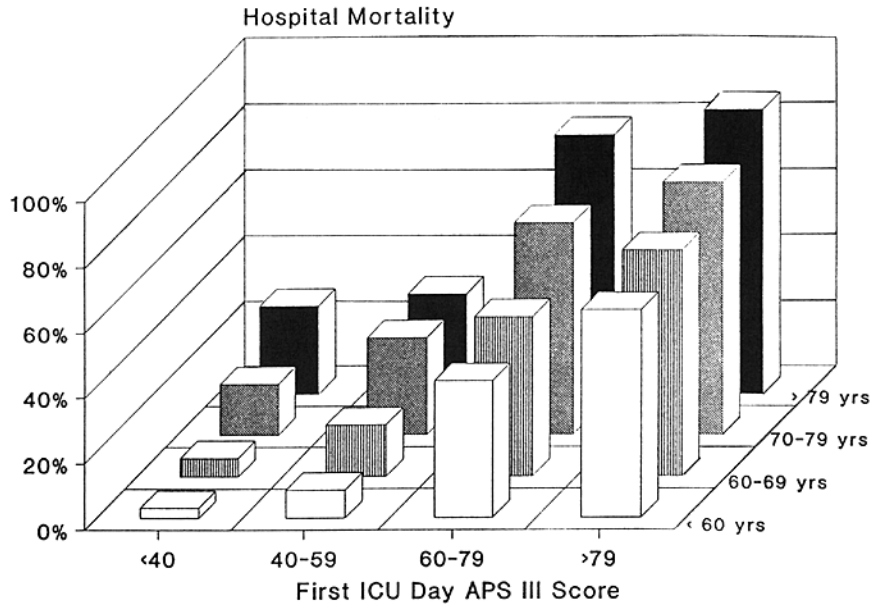


**Figure 6** Hospital mortality by age and admission acute physiology score for patients with ARF due to COPD. Empty bar: age < 60 (N = 166); dotted bar: age 60–69 (N = 250); hatched bar: age 70–79 (N = 277); filled bar: age > 79 (N = 90).

cantly longer ICU stays [8.3 (± 14.1) vs. 5.3 (± 5.8), $p < 0.01$] and higher hospital mortality rates (38% vs. 25%, $p < 0.001$) than patients admitted directly from an emergency room.

A logistic regression model with hospital death as the dependent variable and the first-day predicted risk of death from APACHE III equation ($P_{APACHE\ III}$) as the independent variable produced a receiver operating characteristic (ROC) curve 0.84, at 0.5 cutoff point correctly classifying 84% of ICU patient's outcome and 78% hospital patient's outcome at the time of ICU admission (Table 3). Finally, we compared the predictive power of the APACHE III equation with the APACHE II equation in this group of patients (Table 4).

## IV. Discussion

We studied a group 733 patients admitted to ICUs with ARF associated with COPD from the APACHE III Database, half of whom required mechanical ventilation during the initial intensive care and who had an 81% survival at the time of discharge from ICU. In a meta-analysis of a series of studies in such patients published since 1975, the mean short-term survival rate of ARF due to COPD was 93% (30). A study by Portier et al. reported a short-term survival rate

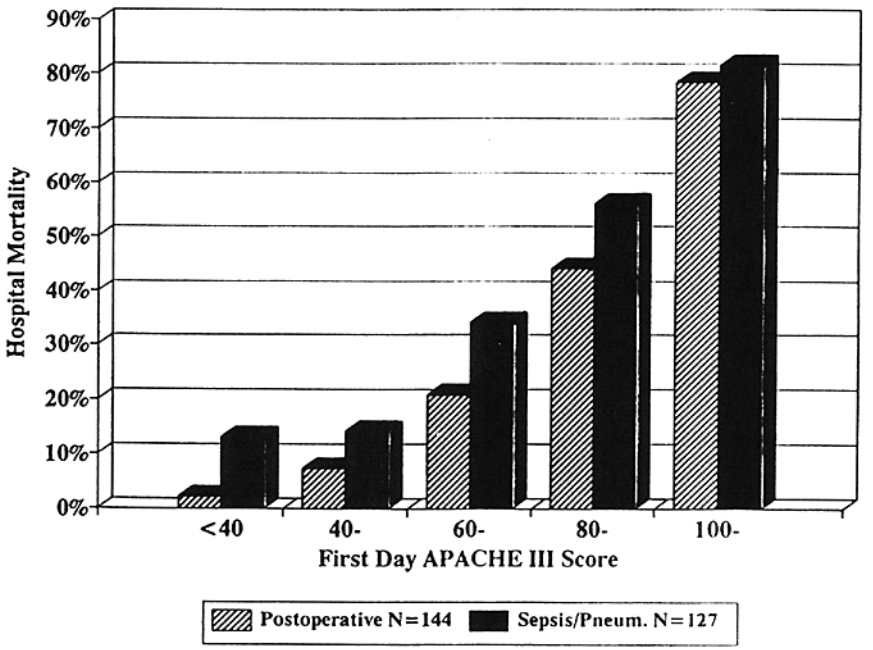


**Figure 7** First-ICU-day APACHE score versus predicted risk of death in two subgroups of patients with ARD associated with COPD. Solid bar: patients with sepsis/pneumonia as precipitating factors; hatched bar: postoperative patients.

of 89% in a patient population which was followed up one month after ICU discharge and which excluded patients with malignant disease (23).

This difference in survival rates between our results and those of others can be explained by differences in patient selection. Our study population was more heterogeneous and more representative of the general ICU population, including all patients consecutively admitted to the ICU with ARF associated with COPD without further exclusion criteria. It included a large proportion of elderly, 40% of patients were 70 years of age or older, with a mean age of 67 (± 11) years, and

**Table 3** Predictive Models for Patients with ARF Associated with COPD

| Model | Dependent variable | ROC | Correct classification (%) |
|---|---|---|---|
| APACHE III Score | Hospital death | 0.833 | 78 |
| $P_{APACHE\ III}$ | Hospital death | 0.843 | 78 |
| $P_{APACHE\ III}$ | ICU Death | 0.847 | 84 |

**Table 4** Comparison of APACHE II and APACHE III Associations with Hospital Death for 733 COPD Patients with ARF

| | APACHE II | APACHE III |
|---|---|---|
| Logistic regression | | |
| ROC area | 0.787 | 0.833 |
| Somers' D | 0.575 | 0.665 |
| Model Chi-square | 168.8 | 239.3 |
| APACHE Score partial Chi-square | 124.5 | 150.7 |
| Least squares regression | | |
| R-squared | 0.219 | 0.297 |
| APACHE T-ratio | 14.3 | 17.6 |

nearly 20% of patients had severe infections such as sepsis and pneumonia as precipitating factors of ARF (Fig. 3). Sixty percent of our patients were transferred to the ICU and had a prolonged hospital stay prior to ICU admission. In addition, patients with severe co-existing diseases, even terminal diseases, such as metastatic cancer and cirrhosis, were included. All patients were followed until hospital discharge. After adjustment for age, severity of illness, and disease category, the observed mortality rates matched predicted mortality rates well (Fig. 5). We therefore conclude that it is important to describe the degree of overall severity of illness of patients in studies of survival prediction. This analysis also shows that the short-term outcome of COPD patients suffering from ARF can be closely predicted in the early stage of hospitalization, soon after ICU admission, with a multivariate predictive instrument such as that used in the APACHE III Study.

In this study, a broad range of abnormalities in the circulatory, renal, neurological, metabolic, and electrolyte systems were associated with ARF. The patients who died tended to be more acidotic, not only because of uncompensated respiratory acidosis but also because of a superimposed metabolic acidosis (2). But they were neither more hypoxic nor more hypercapnic than survivors with preexisting hypercapnic and hypoxemia on ICU admission, a finding consistent with other reports that have found that initial blood gas values have limited prognostic value (5,10,26). It may be that the absolute value of initial blood gas parameters do not reflect an acute attack when there is little knowledge of patients' baseline pulmonary function and prior long-term care. The most severe patients may be intubated in an emergency setting at home or in the emergency room, and their initial blood gases are largely reversible. Nevertheless, the severity of pulmonary impairment might not have a linear relationship to outcome (36).

The nonsurvivors in the present study had a lower mean arterial blood pressure and urine output, higher base deficit and BUN, more severe fluid, acid-

base, and electrolyte disorders, and poorer mental status on admission than did those who survived, probably reflecting the severity of systemic disturbances associated with ARF, such as initial shock and renal dysfunction (Table 2). These abnormalities were related to overall patient deterioration and were present in various combinations and degrees, and all had an important impact on outcome. There are no clear criteria for individual physiological values that clinically discriminate between survival and nonsurvival. For example, mild fluctuations in sodium levels might have no direct physiological effect, but in the COPD patient, low sodium levels accompanied by hypercapnia and hypoxia may reflect a hypercapnia-hypoxia mediated disturbance in renal function (37). Similarly, low albumin alone does not significantly differentiate between outcomes because COPD patients are generally malnourished; but when lower albumin is present with concomitant risk factors, such as older age or infection, it is a poor prognostic factor for survival and weaning from mechanical ventilation. Thus, an estimate of overall physiological derangement and other confounding factors, rather than the presence of ARF alone, is more discriminate than any single measure in determining survival during an acute episode of COPD.

In this study, age was found to be an important prognostic indicator factor both before (Table 2) and after adjustment for severity of illness (Fig. 6) The importance of age in survival is well recognized historically (28,31), and there is a complex relation between age and pulmonary function, comorbidity, activities of daily life, and immunological and nutritional condition. Age may be less important as a prognostic in studies with a small number of elderly patients or in studies that incompletely control for competing risk factors, such as severity of illness.

In this study, immediate precipitating factors for ARF were found to be less important than overall physiological derangement and patient age. The impact of precipitating factors on patient outcome has not been well described in COPD patients suffering from ARF. The specific causes of ARF are essentially unknown (1), and some precipitating factors are difficult to diagnose. For example, pulmonary embolism, which has nonspecific clinical manifestations, has been discovered at autopsy in 20–51% of COPD patients, a much higher prevalence than has been clinically diagnosed. Similarly, airway infections might be contaminated in most COPD patients, a condition that may be clinically inapparent, but the causative role of tracheobronchial microflora in the development of clinically apparent respiratory infection remains unclear. For some patients with ARF, a specific cause for decompensation cannot be demonstrated, making clinically demonstrated precipitating factors less helpful in differentiating patient outcome (2). When the dominant precipitating factors are relatively distinct, such as systemic infection versus major surgery, the difference in mortality rates might become more apparent when sample size is larger (Fig. 7).

Treatment location prior to ICU admission is a potentially important covariate associated with hospital outcome (38). Transfer to an ICU implies a poor

response to prior treatment, development of new complications, and perhaps immunological compromise. In a study of 66 COPD patients with an acute episode of ARF who were treated with mechanical ventilation in an ICU, the 1-year mortality rate was as high as 40%. Much of this mortality was related to a prior prolonged hospital stay and the presence of an associated pathology and malnutrition (39).

Taking all of these prognostic factors into account, including the APACHE III Score (overall severity of illness, age, and chronic health), etiology, and treatment location prior to ICU admission, the APACHE III Prognostic System calculated the Probability of Death ($P_{APACHE\ III}$) on ICU admission from 17,440 ICU admissions and correctly predicted 84% of ICU outcomes at the time of ICU admission and of all hospital outcomes in these 733 COPD patients suffering from ARF, producing a ROC curve of 0.84 (Table 3). There is considerable improvement in the prognostic power of APACHE III compared to APACHE II (Table 4).

Therapeutic interventions, such as mechanical ventilation, were not used as prognostic factors in this study. Although patients requiring mechanical ventilation during initial intensive care have a significantly higher mortality rate than those who do not (Table 2), the frequency of use of mechanical ventilation and survival of intubated patients varied widely (30,40). The characteristics of patients selected for mechanical ventilation were a more important factor in determining prognosis than mechanical ventilation itself. Using mechanical ventilation as a patient selection criterion or prognostic factor is a potential source of bias, since it represents a difference in respiratory management. There is neither a standardized practice nor a clearly defined indicator for institution of mechanical ventilator, except in extreme conditions with clinical respiratory exhaustion, hemodynamic instability, or variations of $Pao_2$, $Paco_2$, and pH (23).

It has been suggested that a changing probability of death after intensive care better reflects the dynamic changes in the pathophysiological process affecting ICU patients (41,42). Patients' response to therapy, duration of mechanical ventilation, as well as later complications, which are usually not considered under life-threatening conditions at the time of ICU admission, might refine and update clinical prediction, especially for patients with the middle range of probability of death, where most of the misclassified patients are located. To accomplish this, a further investigation and assessment of possibility of survival over time is required.

Although patients with ARF due to COPD are frequently admitted to intensive care units, there has been a debate about the clinical management of these patients and a lack of consensus about indications for mechanical ventilation (29,40). This disagreement largely emerged from the poor availability and accuracy of prediction of survival in these patients (10,23). The present study is an attempt to provide a multivariate model that quantitatively describes the impact of overall deterioration of ARF associated with COPD on the predicted outcome of critically ill patients on initial intensive care. Prediction of outcome early in

hospitalization is helpful for making clinical decisions when intubation is controversial, especially in this time of social and economic constraints. Patient functional status, quality of life after hospitalization, and clinical ethics all have to be included into a physician's decision.

The effects of an ARF episode on long-term patient survival, quality of life, and functional status after mechanical ventilation and hospitalization, as well as other factors affecting long-term prognosis such as age, ADL, pulmonary hypertension, cor pulmonale and ventricular failure, number of relapses, nutritional status, and pulmonary function after patients are stabilized (2), were not investigated in the present study and remain an important question to be addressed in future studies. Understanding these factors might help in the determination of the most appropriate long-term care after recovery from ARF. Most of the previous studies of prognosis of ARF in COPD patients have not accounted for the impact of patient's long-term care, such as long-term oxygen therapy, which has shown efficacy in reducing mortality in patients with severe COPD in several studies (1). In a recent study from the French National Association for Home Respiratory Assistance of Chronic Respiratory Insufficiency (ANTADIR) on 1063 COPD patients who were on long-term oxygen therapy, the overall survival was 56.4% at 3 years and 36.8% at 5 years. A prognostic index of survival was built using age, sex, $Pao_2$, $FEV_1$, and Body Mass Index (BMI) (43) that considered previous long-term oxygen therapy and emphasized the effects of physiological reserve on long-term outcome. We expect that the quality of life and long-term survival rates will be improved by using these long-term care techniques.

There is growing interest in alternative modes of treatment of patients with ARF due to COPD, such as noninvasive face mask ventilation, a treatment that has been used in selected patients with acute exacerbations of COPD for whom endotracheal intubation was controversial or contraindicated (44,45). In a trial of 30 elderly patients (45), patients who failed to respond to nasal mask ventilation (NMV) tended to be sicker, with a higher SAPS (Simplified Acute Physiology Score), but did not differ in other clinical characteristics, such as initial blood gas analysis, as compared to patients who responded to NMV. Better stratification and description of degree of severity of illness makes it easier to judge and evaluate clinical effectiveness and efficiency in these trials.

## V. Conclusion

There is a need to predict outcome in patients with ARF associated with COPD. This report demonstrates that patient outcome can be predicted using a prognostic classification system based on detailed physiological data from a representative group of patients. The results of this study indicate that the overall acute severity of illness was the most important determinant of short-term mortality in

patients with COPD suffering from ARF in the APACHE III Study and that better stratification of patient risk and description of the degree of severity of illness in these patients is particularly important for both clinical management and clinical trials.

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# 22

# Oxygen Therapy During Acute Respiratory Failure of Chronic Obstructive Pulmonary Disease

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## I. Introduction

It has been recognized for a long time that hypoxia is the most important threat to life in acute respiratory failure (ARF) of chronic obstructive pulmonary disease (COPD) and that oxygen is the most important treatment (1,2). The main indications for hospitalization (3) of the patient with COPD include:

1. Acute exacerbation of symptoms (dyspnea, cough, sputum production) that have not responded to adjustments in ambulatory care
2. ARF characterized by respiratory distress, hypercapnia, or worsening hypoxemia
3. Acute cor pulmonale with dependent edema, further impairment of exercise capacity, and hypoxemia
4. Complications of COPD such as acute bronchitis or pneumonia, which can present in up to 55% of cases (4)

All of these conditions frequently require the use of supplemental oxygen in order to correct arterial hypoxemia and avoid hypoxic tissue damage (5). Although oxygen treatment is recognized as the one essential component of treatment for hypoxic respiratory failure in COPD, it has also been recognized from the

outset that oxygen causes an acute rise in $Paco_2$ in many of these patients (1,6–9). The resulting acidosis can lead to confusion or coma and often requires the intervention of mechanical ventilation, which brings its own complications as reported in a prospective study of 314 patients undergoing 354 episodes of assisted ventilation (10).

Being aware that hypoxemia is likely to be fatal, whereas the disturbances associated with severe $CO_2$ retention are usually not lethal, it becomes clear that the primary therapeutic objective is to try to achieve adequate oxygenation while, if at all possible, avoiding intubation and mechanical ventilation. Much of the discussion about oxygen therapy therefore revolves around some practical questions:

What are the reasons for the rise in $CO_2$?
Is it possible to predict which patients will suffer an important rise in $Paco_2$ when oxygen is administered?
What modes or concentrations of oxygen should be used?
How high should $Pao_2$ be raised and what rise in $CO_2$ should be tolerated before some kind of mechanical ventilation is instituted?

It should be emphasized that current and future answers to these questions may change greatly because of the recent advent of noninvasive ventilation techniques for the management of hypercapnic respiratory failure.

## II. Pathophysiology

### A. Hypoxemia

Hypoxemia contributes to tissue hypoxia, which is of special concern in the respiratory muscles, whose vulnerability to fatigue is increased, in the myocardium, whose contractility may be impaired and potential for arrhythmias increased, and in the brain, where the ability of the control system to response optimally to the situation may be impaired. Low $Pao_2$ also causes pulmonary vasoconstriction with an increase in afterload to the right ventricle.

The mechanisms for hypoxemia in COPD are discussed in detail in Chapter 8. In acute respiratory failure, hypoventilation and $\dot{V}_A/\dot{Q}$ mismatch are major factors. Also, pneumonia, pulmonary edema, atelectasis or embolism can result in shunts responsible for oxygen resistant hypoxemia.

### B. Hypercapnia and the Effects of Oxygen Breathing

Hypercapnia by itself can be well tolerated, but it is often held that the associated acidemia can contribute to impaired respiratory muscle function and impaired myocardial contractility. For instance, arrhythmias are common during ARF episodes in patients with COPD (11), and their incidence is reduced not only by

correction of hypoxemia but also by correction of acidosis (12). Nevertheless, the role of acidosis can be challenged. Indeed, some studies involving permissive hypercapnia in various settings of difficult mechanical ventilation suggest that profound respiratory acidosis is not mandatorily associated with increased morbidity or mortality (13,14). The reason for that may lie in the facts that intracellular pH (pHic) rather than extracellular pH (pHec) is probably the main determinant of cell function (15–17) and that pHic is poorly reflected by pHec (15,18). Indeed, whereas correction of pHec may take several days, intracellular buffering is much faster: significant acidemia as assessed by arterial blood gas measurements may not correspond to actual intracellular acidosis. Thus, the main determinant of neurological signs associated to hypercapnia could well be the rapid constitution of intracellular acidosis, which would indicate that $CO_2$ narcosis depends more on the rate of rise of $Paco_2$ than on its absolute value. Such a mechanism would well explain the clinical effects of acute administration of oxygen on consciousness and is consistent with clinical experience.

The possible mechanisms of $CO_2$ retention when oxygen is given were well recognized from the beginning:

1. A decrease in minute ventilation, resulting from removal of the hypoxic stimulus to breath (19)
2. An increment in $\dot{V}A/\dot{Q}$ inequalities in the lung (20–22)
3. An increase in $\dot{V}co_2$
4. The Haldane effect (21)

The leading hypothesis, proposed in the 1940s and repeated in most textbooks for the past 40 years, assumed that the patients' ventilatory sensitivity to $CO_2$ was poor so that they had come to depend on the hypoxic stimulus. When the latter was removed, the chemoreceptors defended $Paco_2$ poorly, and $CO_2$ therefore rose. This hypothesis was not tested by actually measuring ventilation until recently, and efforts were made to demonstrate that sensitivity to $Paco_2$ was reduced in COPD but remained unconvincing because of the technical difficulty of a finding a reliable measure of the output of the respiratory centers for COPD patients. Modern evidence suggests that a substantial central response to $CO_2$ is preserved in most patients with COPD, even in acute failure (23). On the other hand, the hypoxic response appears to be substantially impaired in many COPD patients. These observations directly contradict those postulated in the past.

Mechanisms for the effects of oxygen on carbon dioxide are discussed elsewhere in this volume. Here clinical data will only briefly be reviewed.

### *Transient Effects of Breathing 100% Oxygen*

The principle of quantification of the hypoxic drive by measuring the transient decrease in $\dot{V}E$ induced by the substitution of oxygen to room air has first been

applied to patients with stable COPD (24). In such patients, the nadir of $\dot{V}_E$ occurs later than it does in normal subjects, due to the lung inhomogeneity related slower rate of increase in $Pa_{O_2}$. The magnitude of the decrease in $\dot{V}_E$ ranges from 5 to 27% and is significantly correlated with the degree of baseline hypoxemia. In ARF patients, Aubier et al. (25) observed that the course of $\dot{V}_E$ after oxygen administration was similar in magnitude and time course to that observed in stable patients. At the time when $\dot{V}_E$ reached its nadir, $Pa_{O_2}$ was 104 ± 30 mmHg, far above the level that abolishes the hypoxic drive.

### *Steady-State Effects of Breathing Oxygen*

A study of the time course of the changes in ventilation, breathing pattern, and blood gases during a period of 15 minutes after the substitution of pure oxygen for room air in 22 patients with COPD during ARF demonstrated the following results (25): (1) an early decrease in $\dot{V}_E$, which averaged 18 ± 6% (mean ± SE) of the control value due to a decrease in both tidal volume ($V_T$) and respiratory frequency (f), followed by (2) a slow increase in $\dot{V}_E$, so that after 15 minutes of breathing oxygen, $\dot{V}_E$ was back to 93 ± 6% of the control room air value, with both $V_T$ and f similar to control values (25). Despite the rather small difference between $\dot{V}_E$ while breathing room air and at the fifteenth minute of oxygen inhalation, $Pa_{CO_2}$ increased by 23 ± 5 mmHg: the changes in $\dot{V}_E$ and $Pa_{CO_2}$ were not correlated. By the fifteenth minute of oxygen inhalation, $Pa_{O_2}$ averaged 225 ± 23 mmHg.

From these results, it was submitted that despite the removal of hypoxic stimulus by oxygen inhalation, the activity of the respiratory muscles remained great enough to maintain $\dot{V}_E$ at nearly the same level as while breathing room air. On average, the small reduction in $\dot{V}_E$ under oxygen could explain only a fraction (about 5 mmHg) of the total (23 mmHg) increase in $Pa_{CO_2}$. Deterioration of $\dot{V}_A/\dot{Q}$ matching with an increased deadspace–to–tidal volume ratio was considered the major cause of the rise in $Pa_{CO_2}$, with a small contribution of the Haldane effect. This premise was later supported by a multiple inert gas elimination study performed in COPD patients by Castaing et al. (26), which demonstrated the reality of a deadspace increase under an $Fi_{O_2}$ as low as 26%.

In a study by Aubier et al. (27), the increase in $Pa_{CO_2}$ was associated with a decrease in central drive, illustrated by a drop in PO.1, but not with a reduction in $\dot{V}_E$ or changes in breathing pattern (28). During oxygen breathing, the central drive (PO.1) was still higher than in normals (29), and the increased drive to breathe remained supranormal after oxygen administration (25).

### *Predicting the Effects of $O_2$ administration of $CO_2$ Retention*

In order to try to predict which course an individual patient may take when the $Fi_{O_2}$ is increased, Bone (30) studied 50 consecutive patients with COPD and ARF,

13 of whom became stuporous and unable to cooperate under oxygen and required endotracheal intubation because of $CO_2$ narcosis. Based on a discriminant analysis of arterial oxygen tension and pH upon admission, the authors constructed a diagram that separated patients at high risk from those at low risk for $CO_2$ narcosis. They then used the diagram to predict $CO_2$ narcosis in 73 other patients with COPD and ARF who were treated with controlled oxygen. $CO_2$ narcosis developed in 16 patients: 13 (81%) were adequately predicted by the diagram to be at high risk for this complication; only 2 patients (4%) judged at low risk required mechanical ventilation. These data suggest that initial hypoxemia and acidosis are better predictors than hypercapnia for $CO_2$ narcosis.

## III. Clinical Relevance

Severe hypercapnia by itself may be well tolerated when it is chronic. As discussed above, some patients experience confusion, stupor, and coma (i.e., $CO_2$ narcosis) when the $Fio_2$ is only modestly increased (30,31), probably because of rapidly progressing hypercapnia and acidosis not leaving time enough for the intracellular pH to be corrected by buffering mechanisms. This leads some patients to endotracheal intubation and mechanical ventilation, and, from the fact that initial coma and the need for MV are two closely linked criteria, many prognostic studies have only dealt with ARF justifying MV. (see Chapter 21.) Hence, consciousness level has seldom been seen as a prognostic factor (32), as have initial blood gas values.

When the starting point of prognosis evaluation is conservative treatment, the situation is different. Kettel (33) and Sluiter et al. (34) found that the severity of acidosis on admission, expressed as arterial pH, correlates better with survival than does the absolute level of $Paco_2$. Mortality increased markedly if pH was below 7.23. Several studies by the Edinburgh group have looked at the relative importance of high $Paco_2$, acidemia, and low $Pao_2$ for outcomes in patients being managed conservatively during episodes of acute respiratory failure. Warren et al. (35) made a retrospective survey of 157 admissions in 135 patients with acute exacerbations of COPD treated by controlled oxygen therapy where initial $Pao_2$ (breathing air) was below 50 mmHg and $Paco_2$ was above 50 mmHg. The risk of death in any episode increased with the age of the patient but did not correlate with the severity of hypoxemia on admission. Those patients in whom the arterial pH fell below 7.26 during controlled oxygen therapy had a higher death rate than the others. The probability of death was best predicted from an equation combining age and the most severe degree of acidosis that developed during the treatment.

Flenley et al. (36) reported the results obtained in 108 episodes of ARF in 79 patients with COPD studied between 1970 and 1976 and in 103 episodes in 71 patients studied between 1979 and 1983. The severity of the two groups of patients

was similar, with a mean $Pao_2$ of 36 and 37 mmHg and a $Paco_2$of 62 and 60 mmHg, respectively. However, whereas 24% of the patients in the earlier study (1970–1976) died, only 9% of those studied between 1979 and 1983 died. Among the different data for the two groups (cause of decompensation, age, level of hypoxemia, and hypercapnia), a statistical difference appeared with the highest level of hydrogen ion concentration (most severe acidosis), which occurred during the controlled oxygen therapy. Jeffrey et al. (37) recently published a prospective study of 139 episodes of ARF in which they systematically applied the lessons learned from the previous analysis by giving oxygen to raise $Pao_2$ above 50 torr and giving doxapram or mechanical ventilation to try to keep pH above 7.26. Prognosis correlated with the degree of acidemia on admission but not with hypoxemia or hypercapnia, and deaths were more common in those patients whose pH fell below 7.26 during treatment.

## IV. Practical Guidelines

As early as 1960, Campbell (5) suggested that the concentration of oxygen in the inspired air be such that the $Pao_2$ is raised to an acceptable level without totally removing the hypoxic stimulus to ventilation in order to avoid the deleterious effects of hypoxia without producing severe $CO_2$ retention and respiratory acidosis.

*When should the effects of oxygen checked?* Early detailed studies in patients using controlled oxygen therapy led to the formulation of guidelines to help avoid the two dangers of respiratory acidosis and hypoxia (9). The usual and reasonable recommendation is to begin with a smaller concentration of oxygen by mask and follow $Pao_2$ and $Paco_2$ closely, hoping to achieve an acceptable $Pao_2$ without producing an excessive acidosis. Knowing that there is no good way to predict whether or not a given patient will develop a rising $Paco_2$ and whether or not this rise in $Paco_2$ will lead to narcosis, the only accurate way to assess the effect of oxygen therapy is to measure $Pao_2$ and $Paco_2$ repetitively or continuously. Two studies (9,25) of the time course of $Pao_2$ and $Paco_2$ after a step change in $Fio_2$ indicate that the new steady state is reached within 10 or 15 minutes. It is not necessary and may not be advisable to wait longer to determine the immediate results of oxygen therapy.

*What if oxygen administration fails or results in respiratory acidosis?* It has also been suggested (35) that supplemental oxygen treatment in these patients should be guided by the arterial oxygen tension ($Pao_2$) and $H^+$ ion concentration ($\{H_+\}$) and that the aim should be to increase $Pao_2$ above 6.6 kPa (50 mmHg) without causing the $\{H^+\}$ to rise to 55 nmol/liter ($pH < 7.26$). If $\{H^+\}$ rose higher and could not be lowered by adjustment of $Fio_2$, the use of a respiratory stimulant

could be proposed, assisted ventilation being reserved for patients remaining acidotic despite these measures.

In their aforementioned study, Jeffrey et al. (37) applied this concept and used doxapram when oxygen therapy failed to maintain $Pa_{O_2} > 50$ mmHg and pH $\geq$ 7.26 after 2 hours of oxygen therapy at 2 liters/min. Mechanical ventilation was used as a last resort. Doxapram was needed in 25% and mechanical ventilation was used in 3% of cases, leading to a mortality of 13% compared to 7% mortality in 50 episodes when 26% of the patients were ventilated and a 10% mortality in 187 patients when 40% were ventilated artificially. The authors concluded that following those guidelines for controlled oxygen therapy can result in a low mortality without recourse to mechanical ventilation in most of these patients, thus reducing hazards and costs and helping to prevent complications. However, the use of a respiratory stimulant in a situation where the drive to breathe is actually increased (27) has been put in question because overstimulation could precipitate failure of the pump. Current trends in intensive care concepts seem more oriented toward the use, when oxygen therapy is not sufficient, of some sort of noninvasive mechanical support, be it the application of an external PEEP, pressure support, or volume assist, rather than the administration of respiratory analeptics. Fernandez et al. (38) recently demonstrated that noninvasive ventilation could indeed be clinically useful in this setting. In 13 patients presenting with ARF of COPD where oxygen administration produced a rise in $Pa_{CO_2}$ from 68 ± 18 to 92 ± 13 mmHg, they showed that inspiratory pressure support could reverse $Pa_{CO_2}$ and pH back to the values they had before oxygen and avoid the need for endotracheal intubation.

*How should excessive initial oxygenation be dealt with?* It is not unheard of that a patient with COPD in acute respiratory failure is given oxygen in high concentrations at the outset, often in the ambulance on the way to the hospital or in the emergency ward before a definitive clinical assessment has been made. Blood gases may then reveal adequate oxygenation but severe acidosis. In this predicament there is a temptation to reverse the original error in treatment by reducing the inspired oxygen, hoping that the $Pa_{CO_2}$ will revert to the lower level expected if a low concentration of oxygen had been initially given. This tactic is potentially dangerous, however, and should be avoided if there is any concern about the general state of the patient. Indeed, because it takes a relatively long time to reverse the changes in ventilation and gas exchange induced by the high oxygen concentrations, dropping the $Fi_{O_2}$ to a lower level can result in transient hypoxemia deeper than would have occurred if the same $Fi_{O_2}$ had been administered at the outset and sometimes to a very low level (5,39,40). If this tactic is used at all, the $Fi_{O_2}$ should be reduced in steps, the blood gases checked at every step, and the patient monitored very carefully. It may be safer to apply mechanical ventilation, particularly using a noninvasive technique, at least temporarily.

*How should oxygen be administered?* Oxygen may be given by Venturi mask, which delivers gas with a fixed percentage of oxygen at a flow rate considerably greater than minute ventilation, so that the inspired mixture is not significantly affected by the patient's ventilation or breathing pattern. Often, patients do not tolerate the face mask required for this, and pure oxygen may be delivered instead through nasal prongs or a nasal cannula. In that case, the actual $Fio_2$ depends on breathing pattern and on the ratio of nose to mouth breathing. The constancy of $Fio_2$ cannot be guaranteed with this system, but neither can it be guaranteed if the patient with a Venturi mask pulls the whole apparatus off from time to time. With nasal CPAP, the $Fio_2$ may also be difficult to maintain because of leaks or mouth breathing.

*What are the limits of oxygen therapy and conservative treatment?* This question is of particular relevance (41) in view of the increasingly well-perceived risks associated to mechanical ventilation in an aging and therefore more fragile population.

Institution of mechanical ventilation is rarely discussed when the patient is in extremis, in the presence of apnea or agonal respiration, obtundation or uncontrollable agitation, or when acute respiratory failure is associated with severe hemodynamic impairment, whatever its intrinsic cause. Except in such short-term life-threatening situations, there would be general agreement that everything should be done to avoid mechanical ventilation (at least in its classical aspects, namely endotracheal intubation and general anesthesia) because it is associated not only with a series of iatrogenic hazards (42,43) (see Chapter 12) but also with special problems in weaning from the ventilator and in muscle function (44). It is clear that most of these complications are absent with conservative treatment including controlled oxygen therapy (30,45,46).

Between the two extreme situations of life-threatening versus slowly progressive ARF, drawing guidelines for the decision of mechanical ventilation rather than continuation of conservative treatment is difficult. Indeed, particularly in the presence of an advanced underlying disease, clinicians in charge of patients with advanced COPD and ARF must carefully weight the potential advantages of mechanical ventilation against its risks. It appears that major determinants of the prognosis of ARF in COPD are not the acute problems, but the chronic underlying disease (32,47,48). This was first suggested in a retrospective study by Menzies et al. (48), which showed that, in 95 patients with COPD in ARF, survival was associated with premorbid level of activity, $FEV_1$, serum albumin level, and severity of dyspnea. Cor pulmonale on ECG, premorbid hypercapnia, and history of left ventricular failure were more common among those who died. Similar conclusions were later drawn in a prospective manner by Portier et al. (32). At the time where mechanical ventilation has to be decided upon, this type of information may not be available, and the estimate by the physician of the outcome of the patient after MV may be grossly inaccurate (49).

Some recent advances in the management of acute respiratory failure have recently brought new data to light that can help solve the debate. In the past few years, noninvasive ventilation, namely, mechanical ventilatory support provided via a face or nasal mask rather than via an endotracheal tube, has been increasingly applied to the management of respiratory failure, whatever its causes and mechanisms (50–54). It has been shown to avoid the need for intubation, shorten the duration of mechanical ventilation, and shorten the duration of the ICU stay in COPD patients, even elderly patients or those with severe respiratory failure (38,52,55). Recently, a prospective randomized study comparing nasal ventilation and conventional treatment with conventional treatment alone in 60 patients with COPD hospitalized for ARF showed for the noninvasively treated group better results in terms of blood gases, a reduction in the intensity of breathlessness, and a reduction in overall mortality (56). In this study, patients with arterial pH below 7.25 and falling despite aggressive therapy, who would have been intubated and sedated according to previously stated guidelines (36), could leave the ICU after less than a week.

In view of these results, it appears that noninvasive ventilation can fill the gap between conservative oxygen therapy and mechanical ventilation. It seems reasonable to propose noninvasive ventilation as a preliminary step before endotracheal intubation when the limits of controlled oxygen therapy are reached. In COPD patients with ARF too severe to receive conservative treatment alone or in whom oxygen therapy fails to achieve adequate oxygenation without clinically significant worsening of respiratory acidosis, this can either obviate the need for intubation or, in some cases, buy time for the clinician to refine his or her outcome evaluation. Oxygen therapy, noninvasive ventilation, and mechanical ventilation via an endotracheal tube now provide a graded therapeutic arsenal that should improve the necessary fine-tuning of ARF management in COPD patients.

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# 23

## Respiratory Stimulants in Acute Chronic Respiratory Failure

### Analeptics and Related Substances

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Acute on chronic respiratory failure (ARF) is the final common pathway of the various pathophysiological causes that lead to primary failure of alveolar ventilation during the course of chronic obstructive pulmonary disease (COPD). Success in treating acute failure will depend on whether aggravation can be cured while adequate ventilation can be managed by symptomatic treatment and on whether or not irreversible bronchoalveolar destruction has occurred. Symptomatic support of ventilation by other means than mechanical ventilation offers in theory the advantage of cost, availability, and lack of complications linked to intubation and weaning. In hypoxic, hypercapnic patients, ventilation should be controlled so that oxygen administration does not result in a further rise in $[H^+]$ even though $Paco_2$ may remain high (1).

Subsets of ventilatory failure in terms of lung control and function include loss of adequate drive, impaired muscular competence, and excessive respiratory load. The initial rationale for administration of a central respiratory stimulant in COPD patients, particularly during an acute phase, was inadequate respiratory drive. Furthermore, the rise in $Paco_2$ and $[H^+]$ observed during uncontrolled oxygen therapy has been explained by a loss of $CO_2$ drive consecutive to the rise of $Pao_2$, leading to further hypoventilation and an increase in $[H^+]$, thus the logic for stimulation of the respiratory centers.

The usefulness of central respiratory stimulants has long been controversial, first, because the margin between stimulation of ventilation through central neural drive and major neurological side effects is narrow, and second, because it was felt that the rise in $\dot{V}CO_2$ secondary to the supplemental respiratory muscular activity generated by stimulation might induce a further rise in $PCO_2$ and $[H^+]$ that could not be offset by a large enough pharmacological rise in ventilation. Also, because COPD patients generate respiratory pressures five or six times above normal during ARF, a large increase in the force of muscular contraction might precipitate muscular fatigue and thus offset the gain expected on ventilation, given the alinear nature of the dynamic lung compliance curve in these patients. These classic views need to be reassessed in terms of current knowledge about acute exacerbation of COPD (2).

The hypothesis that hypercapnia is induced by depressed respiratory centers does not agree with current knowledge about changes in central $CO_2$ drive in these patients (3). There is even evidence of marked overreactivity, suggesting tentative neural compensation during the acute phase. Management of the regulation of ventilation should integrate the input-output system controlling ventilation, in this instance the coupling of a high internal load with an increased neural drive, and not be limited to central drive stimulation.

Because supplemental stimulation may be ineffective due to the critical role of respiratory muscle fatigue and other than respiratory factors, such as nutritional, ionic, or hormonal factors, the role of pharmacological versus mechanical therapy must be assessed using relevant descriptors. Information on whether neural compensation is adequate, in excess, or insufficient in relation to muscle potential is unfortunately still missing in these patients, in part because of a lack of an adequate set of indexes.

Ventilation-perfusion mismatch and related mechanisms are now recognized to be major contributors to the rise in $PCO_2$ in addition to mechanical lung factors (4). Consequently the potential of pharmacological intervention on local lung regulation must also be integrated in any stimulation strategy and its relationships to neural drive understood.

A drug that could stimulate breathing, improve oxygenation, and lower $PCO_2$ would be of therapeutic benefit (5). The belief that hyperinflated chest, obstructed airways (6) and impaired ventilation-perfusion ratio (7) could compromise mechanical response to an adequately increased neural drive previously led to scepticism towards this therapeutic approach (8–10). Current review of the literature suggests that some room may exist for this approach in strictly defined clinical situations, particularly in subsets of responder patients. Clearly prescription of a respiratory stimulant makes sense only if it can be demonstrated that central activity, even if already elevated, is still inadequate and may be further stimulated with a chance that lung mechanics and perfusion will tolerate the

additional burden (11). Final judgment criteria will include blood gases and $[H^+]$, but energy cost will have to be carefully monitored.

## I. Classification of Respiratory Stimulants

Classification of respiratory stimulants according to chemical composition bears little relationship to mode of action, efficacy, or toxicity (12). Compounds that present no structural analogies, such as doxapram or almitrine bismesylate, may demonstrate some similar functional properties in appropriate experimental settings (13). However, some respiratory drive depressants may be converted to stimulants by the addition of a side chain, suggesting in this instance a possible link between structure and function as is the case for malonyl urea and oxazolidinedione. Also, alkylation of carbamino compounds is a source of respiratory stimulants (ethamivan, nikethamide). Classification of respiratory stimulants is therefore mostly functional and relates to site of action.

Central stimulants act by definition on the central nervous system. General stimulation of the central nervous system can be produced in animals and humans by numerous natural or synthetic compounds. Drugs that induce central stimulation as their most prominent action are categorized as analeptics or convulsants. The margin between dosage for stimulation of central respiratory centers and the production of generalized convulsions is unpredictable but narrow (14). Currently there is no specific and safe stimulant of central respiratory drive. Excitation of the central nervous system can be produced either by enhancement of excitation or by blocking inhibition. Picrotoxin and strychnine are typical blockers of inhibition but have no specific value as selective central respiratory stimulants. Analeptics with respiratory stimulant properties have no action on inhibitory processes and are therefore considered capable of enhancing excitation. None of these are selective central respiratory stimulants, and their ability to stimulate ventilation originates in their properties to enhance excitation rather than to block inhibition of the respiratory centers at drug concentrations lower than those producing generalized central stimulation. Nikethamide (15), pentylenetetrazol (pentanethylenetetrazol), and picrotoxin were the first compounds used in the hope of stimulating ventilation but were demonstrated to have no selective action on respiratory centers; furthermore they are major convulsants (16). They are no longer regarded as therapeutic agents. Remefline, micoren, and ethamivan belong to this category, as do the totally structurally unrelated derivatives of progesterone and xanthines.

Peripheral stimulants act presumably mostly on carotid and aortic chemoreceptors, thus stimulating indirectly the centers. Doxapram and almitrine bismesylate belong to this group.

Doxapram possesses direct central stimulating properties at high enough doses, but almitrine bismesylate does not. Interestingly, both substances may influence the ventilation-perfusion ratio (17). This property, evidenced only in animals for doxapram, is well established and significant for almitrine in both animal models of different species and humans during the course of various respiratory disorders (18,19). Only these peripheral stimulants are still considered for therapeutic use today because of their lower toxicity and more efficient mode of action.

## II. Central Stimulants

### A. Analeptics

Analeptics (central nervous stimulants stricto sensu) were originally used in the treatment of barbiturate poisoning or postanesthetic depression. Mortality rate was 25% during the period of analeptic therapy compared to less than 2% once intubation and ventilation became standard therapy in the intoxicated patients with presumably normal lungs (8). Furthermore, beneficial effects of analeptics reported in postanaesthetic patients are irrelevant to acute on chronic respiratory failure because $P_{CO_2}$ is by no means increased in this condition in a way comparable to the slow buildup of $CO_2$ and $[H^+]$ before failure occurs in COPD patients.

Central neurostimulants have been administrated intravenously in acute or chronic respiratory failure following various protocols. Duration of the stimulation following a single intravenous administration of ethamivan or nikethamide seldom lasts more than 5 or 10 minutes. Because the substance is redistributed after reaching the brain stem and because repetitive doses must be administrated, the concentration limit between respiratory and seizure effects is soon reached. Because convulsive doses are not much larger, permanent monitoring of the patient during intravenous infusion is necessary.

Transient increase in ventilation due primarily to tidal volume have been observed in normal humans and in stable and acute COPD patients following micoren (4 mg/kg/hr), remefline (0.1 mg/kg/hr), ethamivan (4 mg/kg/hr) (20), prethcamide and nikethamide (20 mg/kg/hr) infusion (21). Because groups of patients differed vastly in terms of initial $Pa_{O_2}$, $Pa_{CO_2}$, and $[H^+]$ while breathing air at onset of treatment and because protocols varied so much in published studies, comparison between these drugs is difficult. A moderate but significant rise in $Pa_{O_2}$ has often been observed, but always inconsistently within a group, sometimes with 50% nonresponders (21). Effect of the treatment was never correlated to baseline levels of blood gases. A major difficulty in assessing patients response lies obviously in what different authors have defined as ARF, sometimes incorporating patients with initial $Pa_{O_2}$ as high as 60 mmHg with no elevation of $[H^+]$ (5).

Administration of some central stimulants, in particular ethamivan, resulted

in a rise in oxygen consumption during the course of treatment. This was due to increased general muscular activity, not that of just respiratory muscles, and not to a rise in ventilation, which would have relieved tissue hypoxia (22). The resulting paradoxical fall of $Pa_{O_2}$ had to be compensated for by an increase in $Fi_{O_2}$. Hazards in compensating for oxygen demand in conjunction with the short half-life of these analeptics raised the fear of provoking "peaks and valleys" in oxygenation of tissues that would produce the same hazards found with intermittent oxygen therapy or delivery described by Campbell (23) as a major cause of the deleterious rise of $[H^+]$ in some patients receiving uncontrolled oxygen.

Effects of analeptics on $Pa_{CO_2}$ and $[H^+]$ have been just as inconsistent as for oxygen, with descriptions of fall, no change, and rise in $Pa_{CO_2}$ (8). Said and Banerjee (24) reported that patients with the highest initial $Pa_{CO_2}$ were those who showed the least response when given ethamivan, a finding consistent with a possible discontinuity between the stimulated central activity and the muscular effector capabilities in the most disturbed patients. Also, a rise in $Pa_{CO_2}$ has been reported in relation to a rise in general muscular activity that was greater than the increase in alveolar ventilation (25,26). This has led to the characterization of administration of analeptics in ARF as "whipping a tired horse." Indeed the rise in general, not only respiratory, muscular activity in patients in acute phase is attributable to the proconvulsive side effects of these drugs. In fact, generalized convulsions have occurred in most trials with micoren and remefline (21). Fatalities very likely secondary to the administration of ethamivan have been reported (27). Nikethamide, if administrated intermittently intravenously, is less likely to exhibit such toxicity. However, all central stimulants produce notable side effects, including itching, nausea, vomiting, sweating, and tremor.

Because significant numbers of patients did not respond and because of the high level of intolerance necessitating constant monitoring, these central analeptics have all been discontinued.

### B. Progesterone Derivatives

Levels of progesterone have been related to the increase in alveolar ventilation observed during pregnancy and during the luteal phase of the menstrual cycle (28). Progesterone induces an increase of minute ventilation and hypocapnia in normals and in obese patients after parenteral administration. Medroxyprogesterone, a synthetic derivative that can be administrated orally or sublingually, also stimulates breathing in normal individuals. A significant decrease in $Pa_{CO_2}$ (5 mmHg) at rest and during exercise is noted within 48 hours of drug administration, with a maximum effect at 7 days (29). The substance increases not only minute ventilation but also ventilatory response to hypoxia and to hypercapnia, with important individual variabilities (30–32). The response is unaffected by breathing pure oxygen.

Evidence suggests that progesterone or its derivatives can cross the blood-brain barrier and increase alveolar ventilation by stimulating the brain stem respiratory centers (29). In normal subjects ventilatory stimulation occurs despite a fall in $[H^+]$ in arterial blood and cerebral spinal fluid (29,33).

The treatment of patients with primary alveolar ventilation failure and suffering from obstructive sleep apnea syndrome has proved disappointing in spite of this central stimulation (34). Stable COPD patients with elevated $Paco_2$ have shown a significant fall of up to 8 mmHg of $Paco_2$ after 2–3 weeks of treatment. This fall in $Paco_2$, accompanied by a very moderate rise in $Pao_2$ (5 mmHg) (33,35–38), was observed in only about half of the patients. Results during sleep are contradictory, but one interesting finding was that patients who responded during sleep could be predicted by their ability to lower arterial carbon dioxide while awake (36,39).

Increases in alveolar ventilation have been reported in some emphysematous patients during respiratory failure (40). These findings stress once again the importance of detecting responders and nonresponders to stimulation of ventilation. The slow buildup of action on the brain stem (48 hours) of progesterone derivatives has discouraged their use during ARF.

Side effects in the long term were numerous, including weight gain, anxiety, thromboembolic and cardiac menace, and loss of libido.

### C. Xanthine Derivatives

Aminophylline, theophylline, and caffeine are closely related alkaloids and potent stimulants of the central nervous system. They have been used for many years as central respiratory stimulants to treat Cheyne-Stokes breathing (41,42). Hypoxic ventilatory drive has been found to increase in dogs and normal humans receiving an infusion of methylxanthines at therapeutic doses (43–46) on the basis of a rise in respiratory minute volume. Ventilatory response to $CO_2$ remains controversial (43,44). Most of the contradictory data are related either to subject variability or differences in actual plasma levels, which have not always been measured. In fact, most of the so-called central stimulating properties of methylxanthines are related to direct action on either bronchoreactivity or diaphragmatic function (47–49), two major determinants of minute volume. Methylxanthines can no longer be included in the group of respiratory stimulants.

## III. Peripheral Stimulants

### A. Doxapram

Doxapram [(4-b-substituted ethyl)-3,3-diphenyl-2-pyrrolidididone] was initially described as a central nervous stimulant with powerful respiratory, pressive, and awakening properties (50). Because doxapram has a more reasonable margin of

safety than other analeptics, it has received considerable attention. Its therapeutic ratio—the ratio of the convulsive dose to the ventilatory stimulating dose—is between 20 and 40, whereas for other agents it is 2–4. This high ratio led to the hypothesis that doxapram has a direct selective stimulatory effect on respiratory neurons (51) at doses that do not stimulate nonrespiratory units (52). Such a hypothesis was initially supported by the observation that doses as low as 0.2 mg/kg given to anesthetized cats resulted in an increase of electrical activity of the medullary inspiratory and expiratory related neurons while liminal activation of the cortical and spinal area could only be obtained for doses 10 times higher (52).

However, evidence gathered in dogs demonstrated that in addition to its effects on central respiratory neurons, doxapram also stimulates peripheral chemoreceptors (53). Analysis of the ventilatory response in cats before and after division of the carotid chemoreceptors as a function of the intravenous dose delivered established that doses from 0.5 to 5.0 mg/kg increase firing of medullary respiratory units and minute ventilation. Nonrespiratory units of the brain stem can also be stimulated, but only with doses larger than 5 mg/kg. Even at such large doses the firing of respiratory units remains always greater than that of the nonrespiratory ones (54). Specificity of action on respiratory units is lost after chemodenervation. Doses lower than 5 mg/kg then become ineffective in stimulating respiratory neurons. Rise in ventilation at high dose remains much lower in chemodenervated animals compared to controls.

Changes in ventilation observed for doses ranging from 0.25 to 5 mg/kg in cats (54) are in accordance with direct recording of the integrated phrenic activity (55) for the same dose range (0.2–5 mg/kg). However, after chemodenervation the rise in phrenic activity in the same experimental setting was only detectable for doses larger than 6 mg/kg. This suggested that chemoreceptors were the primary site of action at low doses. The effects produced 2 minutes after intravenous administration of 0.2–6 mg/kg of doxapram were comparable in terms of increase of integrated phrenic activity to the results obtained by varying $Pao_2$ from 35 to 48 mmHg. The subsequent rise in ventilation was mostly a consequence of an increase in tidal volume, although a modest rise (10%) in ventilatory frequency occurred.

The rise in phrenic activity achieved in chemodenervated animals at doses above 6 mg/kg, which remains moderate, is attributable in contrast to an increase in ventilatory frequency, pointing further the difference in mode of action between peripheral and central action of doxapram.

Mechanism of action of doxapram on carotid bodies appears to be related to modulation of ionic currents, in particular of calcium-dependent $K^+$ channels, in type I cells (56).

The drug is capable of inducing a rise in ventilation in normal humans (57). This rise is mostly a function of tidal volume but also of ventilation frequency. The magnitude of the ventilatory response is much greater during hypoxia than during

hyperoxia (57,58). Doxapram also modifies chemoreceptor sensitivity (59,60). In otherwise healthy, lightly anesthetized female subjects about to undergo elective surgery, administration of an intravenous bolus of 20 mg of doxapram increased $V_E$ by 3.3 liters while breathing air, compared to 1.5 liters while breathing oxygen. The ventilatory response was delayed 15.7–23 seconds after switching from air to oxygen. This delay can be analyzed in terms of temporal isolation (61) to suggest that doxapram as a stimulus competes with $Pa_{O_2}$ at the level of the peripheral chemoreceptors. When given intravenously to unanesthetized normal subjects at the therapeutic recommended dosage of 2 mg/min, the drug increased hypoxic sensitivity. The potentiation of the hypoxic drive was analogous to that produced by an increase of end tidal $Pa_{CO_2}$ of 4 mmHg. Hypoxic sensitivity increased even further if doxapram administration was combined with an elevated end tidal $P_{CO_2}$. However, doxapram potentiated the ventilatory response to hypoxia only when such response was already present before administration of the drug. In responders doxapram can also increase the slope of the $CO_2$ response during relative hypoxia at a time when chemoreceptor input to $CO_2$ is minimal. This suggests that doxapram acts at both the central and the peripheral levels, although through different mechanisms.

Again the effectiveness of the drug in respect to $P_{CO_2}$ in a given subject was dependent on a preexisting sensitivity to hypoxia and to hypercapnia. These changes in sensitivity happened in the absence of any alteration of oxygen consumption or $CO_2$ production (62,63). Obviously doxapram may not be equally effective in all patients depending on preexisting sensitivity and its modification induced by clinical status.

In addition to its well-documented chemoreceptor-mediated activity, doxapram may exert some influence on hypoxic pulmonary vasoconstriction. Normal dogs with low sensitivity to hypoxia (nonresponders) demonstrate hypoxic vasoconstriction when plasma levels of doxapram are comparable to those recommended in humans (2 μg/ml) (13,64). This vasoconstriction has also been observed in dogs being given doxapram following experimental lung injury, but it did not result in diversion of blood flow towards better oxygenated lung regions (19). No data are available in humans concerning pulmonary blood flow redistribution.

Although doxapram action while administrated as a bolus is much prolonged compared to a classical experimental chemoreceptor stimulant such as sodium cyanide, its half-life is still short enough to allow easy control of administration, but continuous intravenous infusion is required to obtain permanent action (65). When administration is discontinued in acute patients, return of blood gases to control levels is immediate (66).

Doxapram has cardiovascular properties. It significantly increases cardiac output and pulmonary arterial pressure in animals (67) and in normal humans (68). Cardiovascular effects have been related to activation of the baroreceptors, which

helps explain its hypertensive effects in patients (69). Doxapram also increases arousal. This can be a positive factor in patients more or less narcotized by carbon dioxide. It might be responsible, at least in part, for the rise in ventilation it is credited for because merely asking a more conscious patient to breathe can have the same effect (70). The drug has been found capable of stimulating ventilation in a fair percentage of postoperative patients (71) but not in reversing postoperative hypoxia in patients at high altitude (72), a surprising finding in view of its action in normal humans.

A double-blind trial (73) of five respiratory stimulants (doxapram, nikethamide, prethcamide, amiphenazol, and ethamivan) in patients in acute ventilatory failure conducted on five groups of six subjects each demonstrated that doxapram seemed the most effective in reversing hypercapnia and hypoxemia over the first 24 hours following the 4-hour intermittent drug administration suggested by McNichol et al. (74). Treatment was ineffective on $[H^+]$. Only doxapram produced a significant increase in minute ventilation. Only $SaO_2$ data were available for comparison (75% at onset). Initial levels of $Paco_2$ were around 55 mmHg. No additional oxygen was given during the 24 hours of the trial. The interpretation of data is difficult, particularly because of the small size of each group and the small duration of follow-up of the patients, presumably particularly unstable at this early stage of failure.

Moser et al. (75) addressed the issue of the clinical value of doxapram (2.8 mg/min) not in terms of increase of ventilation, but whether the substance could help counteract the potential depressant effects of oxygen and prevent a rise in $[H^+]$. This study was conducted during the first 2 hours of therapy following admission. The double-blind study included 78 patients ($Po_2 < 50$ mmHg, $Pco_2 > 50$ mmHg) who received controlled oxygen to raise their $Pao_2$ to 60–70 mmHg.

Data showed that stable $Paco_2$ and $[H^+]$ was maintained in 83% of patients receiving doxapram versus 74% in the placebo group. In some patients doxapram infusion was extended beyond 48 hours. Cessation of doxapram infusion after many hours was followed promptly by an elevation of $Paco_2$ back to admission levels. Three percent of the patients finally required intubation in the doxapram group, but the study did not determine whether prolonged infusion of doxapram was efficacious. Indeed, the 2 hours gained, even if used to ensure better drainage and make the patient potentially more cooperative, does not justify the few serious cases of side effects, including hypertension and hallucinations, reported (76). Numerous case reports or studies of small series of patients have repeatedly claimed that doxapram not only could delay intubation but might avoid it altogether (77–82).

The only pertinent studies addressing the issue of doxapram as a substitute for mechanical ventilation, including a retrospective (1) and a prospective approach (83), confirmed the value of $[H^+]$ as an important factor of prognosis for survival. One hundred and thirty-nine episodes of type II respiratory failure were

studied prospectively in 95 patients (83) based on a previous retrospective study. Patients were included in the study on the basis of a $Pa_{O_2}$ below 50 mmHg and a $Pa_{CO_2}$ above 50 mmHg while breathing air. Controlled oxygen therapy (1.3 liters/min by nasal cannulare or 28% by Venturi mask) was instituted to raise $Pa_{O_2}$ above 50 mmHg. A continuous infusion of doxapram (2 mg/min IV) was started and continued for 24 hours if $[H^+]$ rose to 55 mmol/liter at any time during oxygen treatment. Indeed, in this study $[H^+]$ was considered rightfully as a much better index than $Pa_{CO_2}$. Doxapram was discontinued when blood gas data and $[H^+]$ were back within guidelines. Assisted ventilation was implemented if the treatment had not succeeded within that time or if the clinical state of the patient requested it. The study shows clearly the difficulty in adhering to such rigid criteria in an emergency clinical setting, particularly because acidosis may be transient in some patients or because the physician on duty felt compelled to start the prescription before the objective criteria were met. The use of doxapram in a fairly systematic manner based on objective prescription criteria was felt to contribute to a low mortality rate (12%) in the most serious patients. Assisted ventilation was required in only 6% of episodes and deemed appropriate in only 3%. The authors acknowledge that their results on mortality could not be reasonably validated in a clinical context. Their excellent results could have resulted from the extremely careful management of their patients in the particular context of the study.

A preliminary randomized study (84) compared nasal ventilation versus doxapram in 11 subjects. Criteria to define type II respiratory failure in this study were less stringent than those in the study of Jeffrey ($Pa_{O_2} < 60$ mmHg; $Pa_{CO_2} < 48$ mmHg). This study, analyzed on the basis of blood gas data, concluded that nasal ventilation (NIPPV) might be more effective and safer than doxapram. Patients' $[H^+]$ was not stated.

In conclusion, the most pertinent study on doxapram may leave room for prescription of this stimulant in a context of stringent criteria. No study has yet taken into account potential existence of responders and nonresponders, as we do not know how they can be identified. A definitive strategy has yet to be defined to use this drug during acute failure.

### B. Almitrine Bismesylate

Almitrine bismesylate is a piperazine derivative with demonstrated respiratory stimulant action through the peripheral chemoreceptors and possibly via redistribution of blood flow within the lung. The gasometric and ventilatory effects are induced by the diallylamino-triazine moiety of the molecule. The two allyl-amino groups are an absolute necessity for the activity of the molecule (85). It is a stable molecule with long-lasting action: elevation of $Pa_{O_2}$ is sustained in COPD patients for several hours after a single dose (86).

The mechanism of the increase in ventilation following administration of almitrine bismesylate seems to vary with the species; in fact it varies as a function of dose. In anesthetized dogs the increase in ventilation at 3 mg/kg is mostly due to an increase in respiratory frequency (87). In awake cats at a dose of 0.75 mg/kg, the increase is linked almost entirely to an increase in tidal volume (88,89). In humans an infusion of 1 mg/kg increases tidal volume but not respiratory frequency (90,91), whereas both are increased at a dose of 5 mg/kg (92).

The demonstration that this increase in ventilation is due to stimulation of the chemoreceptors has been obtained from direct evidence in animals (93) and circumstantial evidence in humans (94–96). The evidence has been extensively reviewed (87,97). In anesthetized dogs almitrine bismesylate increases the activity of the afferent fibers of the sinus nerve, the inspiratory neurons of the nucleus tractus solitarius, the inspiratory neurons of the nucleus retroambigualis, and the phrenic nerve. Bilateral sections of the sinus nerve in anesthetized rats (98), cats (99), and dogs (87) did not suppress the increase in ventilation, but section of both the sinus nerves and vagi did in rats (98) and dogs (87). A lasting increase of activity in afferent nerves of chemoreceptors of anesthetized rabbits with no interference from baroreceptors, which is reduced by hyperoxia, is observed after intravenous injection of 0.75 mg/kg (100). Because intracisternal (0.2 mg/kg) and vertebral artery (0.02 mg/kg) injections are ineffective (87), direct central stimulation is unlikely. Bilateral carotid denervation in humans has abolished ventilatory response to almitrine bismesylate (101). In patients anesthetized with halothane, the hypoxic ventilatory drive is severely depressed. Almitrine bismesylate restores the hypoxic ventilatory drive, causing a significant increase in $\dot{V}_E$, tidal volume, and mean inspiratory flow while breathing room air. The response is blunted after breathing pure oxygen (102), but only because of an increase in respiratory times. Ventilatory stimulation is depressed by Halothane (103). However, this is due to individual variations offsetting one another as all subjects demonstrate a rise in tidal volume but either a decrease or an increase in respiratory frequency, depending on the individual, resulting in no change in minute volume on average.

Improvement of pulmonary gas exchange in chronic bronchitis cannot be accounted for solely by the analeptic effect of almitrine bismesylate via the chemoreceptors. Individual observations of improved arterial blood gases have been reported in COPD patients without measurable increase in minute ventilation (104), although the drug has no influence on lung mechanics (105). The rise in $Pa_{O_2}$ and the fall in $Pa_{CO_2}$ were greater than those provoked by voluntary hyperventilation in the same patients and thus could not be explained on the ground of ventilatory changes alone, although the duration of the test cannot objectively be compared to the long-lasting effect of hyperventilation induced by almitrine. These discrepancies led to the hypothesis that almitrine bismesylate is capable of modifying ventilation perfusion matching in nonhomogeneous lungs (106–109).

Analysis of data concerning COPD patients breathing normally or mechanically ventilated supports this hypothesis. Administration of a low oral dose of almitrine (1.5 mg/kg) to 18 severe chronic obstructive lung patients ($Pa_{O_2} < 60$ mmHg; $Pa_{CO_2} > 50$ mmHg) in stable condition during a double-blind study produced an increase in ventilation (14%) due to tidal volume and an increase in $Pa_{O_2}$ (5.4 mmHg) with no change in $Pa_{CO_2}$ or $[H^+]$ compared to controls receiving a placebo (7). Blood flow perfusing low $\dot{V}_A/\dot{Q}$ lung units measured by the technique of dilution of inert gases dropped by 4% and was redistributed to lung units with a $\dot{V}_A/\dot{Q}$ ratio between 0.1 and 10. Ventilation distribution remained unchanged. Because the rise of $Pa_{O_2}$ could not be related exclusively to changes in ventilation, it was linked to the redistribution of blood flow from very low $\dot{V}_A/\dot{Q}$ units to lung units with higher $\dot{V}_A/\dot{Q}$ ratios. In this study there was no rise of pulmonary artery pressure either because measurements were done within 1½ hours of injection of the drug or because of the low dose that was ingested.

The same study was repeated in a comparable number of patients admitted for ARF between the fourth and seventh days after endotracheal intubation (17). The drug (1.5 mg/kg) raised $Pa_{O_2}$ by 6 mmHg on average, with a reduction of $Pa_{CO_2}$ after 90 minutes. The main finding was a decrease in the percentage of the perfusion flowing through the true shunt and the underventilated area, demonstrating a reduction of gas exchange abnormalities following almitrine bismesylate administration. This study was designed to eliminate external ventilatory effects and did not demonstrate efficacy of the drug during mechanical ventilation of COPD patients. It confirms that almitrine bismesylate improves arterial $P_{O_2}$ in chronic hypoxemic patients, including during the acute phase, even in the absence of ventilatory stimulation (106,108,110–112). The enhancement of hypoxic pulmonary vasoconstriction (113,114) is considered instrumental in explaining the redistribution (109,115) consecutive to administration of almitrine bismesylate. Stimulation of peripheral chemoreceptors may lead to neurogenic pulmonary vasoconstriction (116,117). It could be that almitrine bismesylate induces pulmonary vasoconstriction via its stimulation of carotid and aortic bodies (87). COPD patients who have been chemodenervated do not demonstrate gas exchange responses to almitrine (101), but no data on pulmonary hemodynamics were available in this study. However, none of the studies of Castaing et al. (7,17,118) showed any rise in pulmonary vascular resistance during acute failure. Normal pulmonary pressures have also been reported in chronic patients over a 1-year period (119).

Administration of a 15-minute perfusion of almitrine bismesylate to both chemodenervated (carotid body and aortic arch) and ventilated sheep with control $Pa_{O_2}$ ranging from 50 to 150 mmHg demonstrated a significant increase in $Pa_{O_2}$ with no change in $Pa_{CO_2}$ or $[H^+]$ and a very moderate rise of pulmonary vascular resistance (120). The drug may therefore have a distinct action via chemoreceptors and via lung receptors on local hemodynamics (121).

The vasoconstrictive effects of almitrine in normals and COPD patients do not always support the hypothesis of a durable reinforcement of an hypoxic pulmonary vasoconstriction (109). The relative time constants of the initial vasoconstriction and of the long-lasting increase in $Pa_{O_2}$ do not coincide. This dissociation has been confirmed in anesthetized dogs breathing spontaneously (87) and in numerous isolated lung preparations. When pulmonary arterial pressure is raised by alveolar hypoxia in isolated perfused lungs of rats (122), ferrets, or in chronically hypoxic rats (123), almitrine bismesylate causes a further rise in pulmonary artery pressure, which is of short duration with a secondary return to base-line level. The same observation applies in separately ventilated lobes of ferrets, cats, and dogs. In anesthetized and paralyzed dogs with normal lungs, almitrine enhanced hypoxic vasoconstriction. This increase in pulmonary vasoconstriction was maximal at lower $Fi_{O_2}$ (115). However, the arterial $P_{O_2}$ did not change during infusion of the drug, but the dose was low (0.1 mg/kg). In this instance there was both a lack of effect of the drug in modifying $\dot{V}_A/\dot{Q}$ relationships and $Pa_{O_2}$. An explanation for these negative findings might be that in normal dogs there are essentially no areas of low $\dot{V}_A/\dot{Q}$ to begin with, and therefore almitrine bismesylate would not be expected to improve $\dot{V}_A/\dot{Q}$ and $Pa_{O_2}$. It is the degree of initial $\dot{V}_A/\dot{Q}$ inhomogeneity prior to giving the drug that would determine the rise in $Pa_{O_2}$.

Because the response is observed in vivo, in isolated lungs after section of the vagi and sinus nerve, and after chemodenervation in animals, a regional effect on the lungs is likely. In isolated rat lungs, verapamil, a calcium channel blocker, suppresses vasoconstriction, an argument in favor of local receptors. Suppression of prostanoids derived from the cyclooxygenase pathway by indomethacine treatment delays the return of pressure to baseline in dogs, suggesting either an enhancement of vasoconstriction over time or inhibition of vasodilator release mediated by prostaglandins. Vasoconstriction could not be explained by thromboxane (a major vasoconstrictor) release in sheep (124), but late release of prostacyclinlike material (a major vasodilator) or metabolites has been identified in cats, rabbits, and sheep (124,125). A balance over time of an unknown vasoconstriction factor and of prostacyclin, a vasodilator, might explain the apparently conflicting data on the relationship between $Pa_{O_2}$ and vasoconstriction due to almitrine. Although prostacyclin release is generally a nonspecific lung response to vasoconstriction, the hypothesis of an elective enhancement of the response to hypoxia in low $\dot{V}_A/\dot{Q}$ zones with redistribution of flow to better perfused zones would fit experimental data in animals and humans. Mechanisms of direct action on the lungs remain unknown, but some evidence of direct fixation of $^{14}C$-almitrine on endothelial cells exists (126).

Almitrine bismesylate has been advocated for treatment of COPD and has been shown to increase $Pa_{O_2}$ (121) in these patients over long periods of time. The beneficial effects of higher $Pa_{O_2}$ in terms of survival or of incidence of acute

decompensation during a 1-year follow-up of an initial group of 600 patients were not demonstrated (127,128). Long-term administration of the drug has lost favor due to the incidence of late peripheral neuropathies (127,129) and because it tends to increase pulmonary artery pressure during exercise in some patients (130).

Experience of delivery during ARF is limited. Tenaillon et al. (111) in an uncontrolled, nonrandomized study confirmed the ability of the substance (0.5 mg/kg intravenously over 1 hour) to increase $Pa_{O_2}$ with no effect on $Pa_{CO_2}$ or on cardiac output in a group of 13 ventilated patients 48 hours after intubation, although $Pa_{O_2}$ was elevated due to high $Fi_{O_2}$. The primary aim of this study was not to advocate the use of almitrine during acute episodes but suggested, albeit indirectly, that its administration might help reduce $Fi_{O_2}$ during mechanical ventilation. Naeije et al. (107) gave the drug intravenously (0.25 mg/kg in 30 min) to 12 decompensed patients ($Pa_{O_2}$ = 50 mmHg; $Pa_{CO_2}$ = 67 mmHg; pH = 7.29) sometime during the first 2 days after admission. Increase in blood oxygenation occurred before any variation in ventilation of $Pa_{CO_2}$. It was larger than expected from the increase in alveolar ventilation. Ventilation rose due to tidal volume since there was no variation in respiratory rate. Pulmonary hypertension was aggravated, and four patients experienced malaise and exacerbation of dyspnea, forcing interruption of the protocol without delay. Systemic hemodynamics were unchanged. Side effects possibly were the result of the high dosage used in these patients. This dosage has been reported to be too high for stable COPD patients (131,132). Touaty et al. (133), in 1980, used almitrine bismesylate at a dose of 0.5 mg/kg but over 6 hours in a double-blind study of 24 patients (baseline $Pa_{O_2}$ = 63 mmHg; $Pa_{CO_2}$ = 46 mmHg) receiving oxygen at low flow, but these patients would hardly be considered in an acute stage by current criteria. Results in terms of ventilation, blood gases, and hemodynamics were comparable to previous studies. Only one patient had to be withdrawn from the almitrine group for intolerance. The patient suffered from hyperventilation with further rise in $Pa_{O_2}$ and drop in $Pa_{CO_2}$, suggesting overaction of the drug. Although no patients were intubated in this group compared with four in the placebo group, this was not statistically significant. Bardsley et al. (134) randomly allocated 23 patients admitted to the hospital for acute exacerbation of ventilatory failure ($Pa_{O_2} < 60$ mmHg; $Pa_{CO_2} >$ 45 mmHg) to receive oral almitrine (100 mg once daily at onset of treatment) or placebo in addition to conventional treatment. The results showed no benefit from oral almitrine, but plasma almitrine concentrations were often below the optimum therapeutic range, suggesting impaired drug absorption.

Obviously administration of almitrine bismesylate at the onset of or during acute respiratory failure cannot be based on such limited evidence. The drug has failed to meet its target in treatment of COPD patients because of major side effects and possible overdosage. It may deserve reexamination during acute episodes. Although this is currently being done during ARF secondary to other etiologies, in particular during acute respiratory distress syndromes, conclusions

from these trials should not be extended by any means to COPD patients who do not have normal lungs to start with.

## IV. Conclusion

The potential value of doxapram and almitrine bismesylate, the two agents that may be used for stimulation of respiration during ARF of COPD either through peripheral chemostimulation or putative lung receptors, cannot be assessed because of lack of sufficient data. However, guidelines for future studies may be drawn.

Because a true ineffectiveness of central respiratory drive relative to the effector potential has still to be demonstrated among this type of patient, the rationale in favor of use of central analeptics is limited until subgroups of patients that may require such stimulation can be readily identified. In any case, central nervous system analeptics are currently unacceptable because of the narrow safety margins and unconvincing performance demonstrated in the small, ill-defined groups in which they have been tested. Most of these substances are no longer clinically in use, and their use for research purposes should be strictly monitored in view of the risks involved.

Peripheral stimulation of chemoreceptors and direct lung action via ventilation perfusion rearrangement offer more credible alternatives to mechanical ventilation in ARF of COPD. Limited studies on doxapram and almitrine bismesylate suggest that some room may exist for such therapy. Even though a double-blind multicentric study might help to determine this, two points still need to be addressed.

First, we lack the methodological tools to evaluate the capacity of any individual to respond favorably to such stimulation (2). It has been clearly demonstrated that for normal humans there are responders and nonresponders to doxapram, just as we know that there are responders and nonresponders to an hypoxic stimulus in normal animals and humans. It is obvious that such individual response exists in patients and could possibly be exacerbated.

Second, because the pathology of acute failure is so diverse, respiratory failure results from an array of possible mechanisms of which chemoreceptor sensitivity and ventilation perfusion ratio rearrangement are only two. We need to better quantify in a responder patient, depending on its patholophysiology, the amount of stimulation he or she can sustain without outrunning the corresponding effectors.

In view of these considerations, conclusion about the possible benefits of peripheral respiratory stimulants cannot be drawn until further progress is made in terms of evaluation methodology. Because intubation remains so easy in the setting of the intensive care unit and provides reasonable control of the acute

phase and because a medical approach to these patients would require heavy monitoring not necessarily available outside of the intensive care unit, interest in these drugs has diminished.

Indeed, studies have consistently demonstrated that doxapram may buy time for the patient before intubation. Yet if delaying intubation is the only beneficial effect, use of doxapram may not be advisable.

Current changes in resuscitation code status and considerations of cost-effectiveness may require reassessment of specific respiratory stimulants, albeit in the context of individual responsiveness to therapy. In particular, a reassessment in light of the recent procedures of external ventilatory support (135) seems appropriate.

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# 24

# Chest Physiotherapy from Chronic to Acute Respiratory Failure in Chronic Obstructive Lung Disease

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## I. Introduction

Patients with chronic obstructive pulmonary disease (COPD) are at increasing risk of episodes of acute respiratory failure (ARF) as their baseline pulmonary function declines over the years. Most physiotherapy programs for COPD have had "rehabilitation" as their goal: to improve the baseline functional state of the patients in the hope that this would reduce the likelihood of episodes of ARF, reduce time spent in hospital, and prolong life. Several studies have been published that suggest that comprehensive programs can indeed reduce hospitalizations and costs (1–4), prolong life (5,6), and improve quality of life. Regrettably, there has not yet been a well-controlled prospective trial to substantiate these optimistic conclusions (7).

Comprehensive programs have many components, ranging from psychotherapy and education to adjustments of drug regimes, exercise prescription, and oxygen. No studies have evaluated the importance of individual components of the programs for the final outcome with the exception of oxygen, which reduces long-term mortality. In spite of participation in a good program, 93 of 143 patients reported by Sahn and Petty (5) eventually died of COPD. Not surprisingly,

rehabilitation programs seem to impart most marked benefits to patients with less severe disease.

In this chapter we will discuss physiotherapy techniques one by one, from those commonly employed in chronic, stable patients to try to prevent ARF and to those that may be considered for use during ARF.

## II. Techniques That Could Improve Function in Severe Stable COPD

### A. Airway Clearance

Chest physical therapy (CPT) includes postural drainage, chest percussion, vibration with or without instrumental support, cough, and forced expiration techniques (8,9). The goal of these commonly used techniques is to accelerate the clearance of secretions from the airways. Conflicting data do not give a definitive answer on their true utility. Appreciable changes in pulmonary function in stable COPD have been observed only when the amount of sputum exceeds 30 ml/day (10–12), as pointed out by Murray (13). Cough is able to move airway secretions from peripheral to central airways (14), although in very severe COPD patients, retrograde motion of secretions has been described (15). The forced expiration technique alone is able to move airway secretions (16) with no added value of posture and high-frequency vibration (17). Slow expiration over a large volume can also improve the clearance of peripheral and central airways.

Postural drainage alone does not seem valuable in chronic bronchitis (18). There are theoretical and experimental arguments for applying external or internal vibration with a given frequency (19,20), but when combined with other techniques such as posture, cough, and breathing maneuvers, the benefit of vibration seems negligible (21). Expiration against a variable expiratory pressure (CPAP) has been proposed (22,23) but has no effect on regional lung clearance evaluated by isotope scanning techniques (24). After some initial enthusiastic reports on long-term effects in COPD of CPT (25), more recent studies have not been able to demonstrate a definite effect of CPT as reduction of either acute exacerbations or functional deterioration (26,27).

### B. Breathing Pattern

Even in the chronic stage, when compared to normal subjects, patients with airway obstruction show rapid shallow breathing with increased drive to breathe (28,29), probably contributing to dyspnea (30). This tendency is stronger in hypercapnic patients when compared to normocapnic ones (28,29). Rapid shallow breathing has the obvious physiological disadvantage of increasing the ratio of deadspace to tidal volume and thus increasing wasted ventilation. Chest physiotherapists have therefore tried to lower the respiratory frequency and increase tidal volume in the

hope that this would improve gas exchange (31–34). Earlier works looked for improvement in lung mechanics or dyspnea (35,36). More recently, effects on the respiratory muscles have been considered. At least three techniques may induce breathing pattern changes: controlled slow deep breathing, pursed-lips breathing (PLB), and diaphragmatic or abdominal breathing (AB) (37).

The assumption underlying all attempts to modify breathing pattern is that the respiratory control system of the patient is behaving in a way that produces less than optimal use of respiratory muscles or a less than optimal choice of tidal volume inspiratory or expiratory time. In that case the patient would be better off if the control system were overridden, and a more rational pattern of breathing imposed. We do not yet understand the complex predicament of the patient with severe COPD well enough to be really certain on theoretical grounds when the patient has chosen a poor strategy for breathing or how to improve it. Recommendations for overriding the natural pattern of breathing therefore need to be validated by practical demonstrations of benefit to the patients.

### *Slow Deep Breathing*

Some physiotherapists have trained subjects to breathe slowly and deeply. Many studies have demonstrated improvements in alveolar ventilation while the patient is doing the maneuvers (31–35, 38–41). On the other hand, some investigators stressed that work of breathing can be increased (32,42,43).

More recently, Bellemare and Grassino showed that patients with severe COPD became distressed when obliged to breathe slowly and deeply. This was associated with an increase in tidal swings in transdiaphragmatic pressure that brought the pressure time index of the diaphragm close to the fatigue threshold and produced EMG changes of fatigue (44). These observations suggest that, for many COPD patients, the choice of small tidal volumes may be based on an essential compromise between maintaining the efficiency of gas exchange and preserving the integrity of respiratory muscles.

### *Pursed-Lips Breathing*

Pursed-lips breathing (PLB) is of particular interest because patients often adopt this behaviour spontaneously, especially when they are very short of breath. They inhale through the nose and then exhale slowly through pursed lips (45).

Patients with PLB are severely dyspneic, have somewhat variable breathing patterns, and are hard to study. Various reports of investigations of small sets of patients have given variable results. Studies in which patients who do not naturally do PLB but are trained to do it artificially should be distinguished from ones where the patients have begun PLB on their own, presumably to relieve an unpleasant sensation or to produce some physiological improvement appreciable to their own control system.

Patients trained to do PLB voluntarily have been reported to show an improvement in oxygen saturation (46), increase in tidal volume, decrease in frequency, prolonged expiratory time, reduction in $T_I/T_{TOT}$, and reduction in transdiaphragmatic pressure-time index with no change in tidal swings in transdiaphragmatic pressure (47). Changes in esophageal and gastric pressure swings also suggested an increase in use of intercostal/accessory muscles and perhaps abdominal muscles. The maneuver actually performed by these patients was thus a combination of PLB, slow deep breathing, and AB. Older studies, more limited in scope, found some reduction in expiratory flow with no change in end-expiratory volume (39,48).

Patients who naturally use PLB have been studied by asking them to breathe with open mouth and comparing various physiological parameters in the two modes of breathing. These have given variable results, some showing an increase in oxygenation or small changes in breathing pattern with PLB. Conflict between results in various reports of small series makes it unclear which of these observations is reliable. The meaning of these investigations has been cast further in doubt by the finding that many patients with natural PLB have little change in the resistance of their upper airway on shifting from PLB to open mouth breathing. That is, they seem to replace the resistance at the lips with another constriction somewhere in the pharynx.

It is not clear that PLB should be expected to produce changes in gas exchange, expiratory time, or respiratory muscle use in patients with severe dyspnea. The patients are probably exhaling along their maximum flow-volume curve, with flow limitation and a very high resistance in their intrathoracic airways. Under these circumstances the simple interposition of a small downstream resistance (measured at 2–5 cm $H_2O$/liter/sec), does not change the resistance of the whole airway, and would not have any influence on work of breathing, lung volume, or expiratory time. Its most important effect would be to move the site of flow limitation downstream towards the mouth. Flow limitation in the intrathoracic airways is associated with high turbulence and vibration of airway walls, which may very well be uncomfortable for the patients. The main advantage of PLB may simply be to reduce this discomfort.

### *Abdominal Breathing*

Abdominal breathing (AB), sometimes called diaphragmatic breathing, was advocated early by Barach (49) as an attempt to improve diaphragm excursion in patients with hyperinflation, whose diaphragms are thought to be ineffective because of their flatness (50–52). Patients are asked to expire actively by contracting the abdomen and may be helped by a physiotherapist placing a weight on the abdomen (49,53). This may push the diaphragm upwards, lengthening it and giving it a better curvature. The abdomen then relaxes in inspiration while the

diaphragm contracts. Movements of the diaphragm are enhanced, and some authors have described an increase in abdominal expiratory pressure as well as end-expiratory volume (54).

Basing their analysis on measurements of swings in gastric pressure and pleural pressure during quiet breathing in 45 stable cases, Martinez et al. (55) concluded that COPD patients tend naturally to change their pattern of ventilatory muscle use from one where most of the effective ventilatory pressure is generated by the diaphragm to one where most of the pressure is generated by rib-cage inspiratory muscles with a significant contribution by the expiratory muscles. The changes correlate directly with the degree of airways obstruction (FEV, % predicted) and hyperinflation (FRC, % predicted). Other studies have confirmed the increase in activity of scalene and sternocleidomastoid muscles (56) and abdominal expiratory muscles (57).

Abdominal contraction may well force the diaphragm up into a more curved shape and lengthen its fibers at end-expiration. This could be associated with a decrease in end-expiratory volumes, but in patients with severe expiratory flow limitation, that may not be easy to achieve, and the upward movement of the diaphragm may be partly accommodated by expansion of the rib cage. Whether the active contraction of the diaphragm is aided by the abdominal muscles depends on when the diaphragm is activated. Abdominal muscle relaxation in early inspiration may in fact allow the diaphragm to fall back to its usual disadvantageous position before it begins to make its own efforts. Under these circumstances, some of the swing in transdiaphragmatic pressure with breathing may be due to passive stretching, making it difficult to interpret pressure data in terms of work performed by diaphragm muscle fibres. Ninane et al. (58) have argued that, in normal subjects at least, contraction of abdominal muscles in expiration does not in fact confer any mechanical advantage on the diaphragm.

Some older studies have claimed that AB improved respiratory muscle endurance and strength (35,41,59,60), but this was before valid methods were developed to make such assessments. Patients doing abdominal breathing force their chest walls far from their relaxation configuration, implying increased work of breathing (61,62). Also, paradoxical chest wall movement can be observed in AB in patients who do not show this in natural breathing (61).

The most important effect may simply be to shift some of the respiratory work from the diaphragm to other respiratory muscles. We have seen one patient with severe COPD who may have achieved the same effect by using his arm muscles. He contrived a belt that circled his abdomen snugly and could be tightened and loosened by means of a lever. During episodes of severe dyspnea this ingenious person was able to obtain considerable relief by throwing the lever back and forth with each breath.

A different advantage of the method might be to improve gas exchange by changing the regional distribution of ventilation. Redistribution is possible in

normal subjects (63–66) but is much harder to be sure of in COPD patients (34, 67–70).

*Conclusion*

In general, imposed changes in breathing pattern can make short-term (during the time of supervised breathing pattern change) differences in some physiological parameters. Some of these may be beneficial, but they may be outweighed by detrimental effects that are harder to measure, such as stress on the respiratory muscles. It is not known if the training results in any long-term change in the natural breathing of patients once they stop consciously directing the pattern of each breath. The most important use of the maneuvers seems to be during episodes of severe dyspnea. In these circumstances the maneuvers may simply permit the patients to feel they are able to control the situation, reduce their anxiety, and prevent panic.

### C. Body Position

*Supine or Head Down*

In chronic respiratory disease, Barach and Beck (71) were the first to observe that patients in the head-down position experienced less dyspnea and attributed this to a decrease in respiratory effort and reduction in the use of the accessory muscles of breathing. They also observed an approximate 2-cm increase in diaphragmatic excursion. In this position and with abdominal weights Gayrard et al. observed a 3-cm headward displacement of the diaphragm without any additional increase in diaphragmatic excursion during tidal volume breathing.

It is well known that in normal subjects the supine position implies a decrease in the functional residual capacity with probably a better length of the diaphragm and therefore a possible improved mechanical effectiveness (72). Such a decrease in FRC is either not observed in COPD patients (73) or is found to be quite modest (74). Sharp and coworkers showed that a subgroup of COPD patients with hyperinflation and paradoxical inspiratory inwards motion of the abdomen experienced some relief in dyspnea in the supine position (75). When compared to the sitting and standing position, this position induced a substantial increase in the ratio of phasic changes in transdiaphragmatic pressure ($\Delta$Pdi) to amplitude of the EMG of the diaphragm ($\Delta$Edi), indicating improved effectiveness of the activated diaphragm in this position.

*Leaning Forward*

When the respiratory pump is considerably impeded patients often adopt a sitting position with the trunk bent forward 20–45° from the vertical position, supporting the position comfortably with hands or elbows on their knees (61). This appears to

allow the pectoralis major and minor, the latissimus dorsi, the serratus anterior, and the lower part of the trapezius to contribute to respiration (76).

Sharp et al. studied COPD hyperinflated patients who experienced relief of dyspnea in this position and observed results in $\Delta Pdi/\Delta Edi$ similar to the supine position (75). Willeput and Sergysels showed that in going from a sitting erect to a sitting forward position, COPD patients probably changed their end-expiratory level very little. During tidal volume breathing abdominal displacement as assessed by magnetometers is decreased, while gastric pressure is considerably increased, suggesting that the abdominal compliance is reduced in this position. Tidal volume is largely achieved by a thoracic displacement probably by means of the greater abdominal pressure "driving" the lower part of the rib cage via a larger zone of apposition of the diaphragm.

### D. Intermittent Positive Pressure Breathing

Intermittent positive pressure breathing (IPPB) was long in vogue for chronic lung disease. Patients would come to the hospital at regular intervals and sit for a few minutes breathing a nebulized bronchodilator from a positive pressure ventilator. Long-term efficacy was assessed in a large controlled trial, which found no detectable effect of this expensive practice on survival, decline in $FEV_1$, or hospitalization (77). The effects of IPPB on breathing pattern and dyspnea were not studied.

### E. Respiratory Muscle Training and Rest

An enormous amount of work has been done in the field of the pathophysiology related to the respiratory pump both in normals and in COPD, which has been reviewed by Derenne et al. (50–52) and brought up to date elsewhere in this book.

With impeded ventilation and especially with hyperinflation, the respiratory pump works with a high $Pmus/Pmus_{max}$ and thus $Ppl/Pdi_{max}$ and $Pdi/Pdi_{max}$, due to both an increase in Ppl to overcome airway resistances and a decrease in $Pdi_{max}$ (mostly due to the shortening and flattening of the diaphragm). These ratios have been related to dyspnea (the harder the pump works, the higher the likelihood the patients will experience dyspnea) (78). Furthermore, a pressure time index (defined as $Pdi/Pdi_{max} \times T_I/T_{TOT}$) of a certain value defines a threshold above which the respiratory pump may fatigue or even fail (64). This threshold may be reached in severe COPD patients simply by changing the breathing pattern.

In theory, physiotherapy could help reduce dyspnea or avoid fatigue or improve alveolar ventilation by improving $Pmus/Pmus_{max}$ or $Pdi/Pdi_{max}$. Some changes in breathing pattern and body position as described above can improve the ratios by reducing the numerator (Pdi, Ppl, Pmus) or by making the muscles more effective as pressure generators. On the other hand, some maneuvers, such as slow deep breathing, tend to worsen the ratios and may aggravate dyspnea.

Another approach is to change the denominator by improving maximal muscle strength or change the fatigue threshold by improving muscle endurance. In the event that respiratory muscles have actually become fatigued (79) and therefore have lost some of their strength, rest could be beneficial.

### *Respiratory Muscular Training*

Leith and Bradley (80) were the first to demonstrate the possibility in normal subjects of increasing both strength and endurance of the respiratory muscles by specific training techniques. Smith et al. (81), reviewing this field when applied to COPD, identified 17 relevant studies out of 73 and summarized the results in a metaanalysis. Some positive results have clearly been obtained on endurance or strength scores and other parameters, such as walking distance, peak $V_{O_2}$, and dyspnea. The authors pointed out that such techniques require accurate control of the breathing pattern, the pressure developed, and also the ventilation achieved. Results are also affected by the mode of training and its duration, frequency, and intensity. Overall the authors conclude that there is "little evidence of important effects on outcomes of greater relevance to patients including functional exercise capacity and quality of life."

Participants in the workshop on respiratory muscle fatigue (82) were likewise not convinced of the value of training respiratory muscles and specified that "training of muscles already being driven at the limit of their capacity may produce myopathic changes well recognized in overtrained athletes, recovery from which can be prolonged." Furthermore, as pointed out by Rampulla and Ambrosino (83) undesirable effects during training programs have been identified, such as hypoventilation (84) and increase of transmural artery pressure to hypertensive values (85). Training or rehabilitation programs must be designed to avoid the possibility of injury or fatigue of the patient's respiratory muscles.

Thus inspiratory muscle training should not be included in rehabilitation programs for all patients. There is a real need to define subgroups that could benefit from these techniques. One of the most interesting goals (86) of respiratory muscle training—to prevent patients from developing acute respiratory failure—remains. Training programs must be designed to avoid causing damage or fatigue of the muscles.

### *Respiratory Muscle Rest*

The hypothesis justifying respiratory muscular rest is that "chronic respiratory muscular fatigue" (79) may explain respiratory muscular weakness, rapid shallow breathing, and hypercapnia. With this in mind, putting the respiratory pump at rest could reverse the consequences of chronic fatigue.

It is important to emphasize that most authors no longer support the chronic respiratory muscle fatigue concept. Rochester, in a recent editorial (87), reviewed

the important contribution of Bégin and Grassino (88) regarding the physiopathology of chronic hypercapnia. From a group of 300 COPD patients, hypercapnia was correlated with VD/VT, $FEV_1$, lung resistance, total lung resistance (RL), and finally RL/maximal inspiratory pressure (MIP) ratio. The authors found that no single variable or combination of two could explain more than 35% of variance of $PaCO_2$. In the chronic stage no patient exceeded a PTI that could have induced fatigue. The conclusion is that probably one of the adaptive mechanisms is to allow a reduction in VT TO AVOID FATIGUE EVEN IF THIS LEADS TO INCREASED $PaCO_2$.

A preliminary report of an uncontrolled study from Braun and Marino (89) was very enthusiastic, showing improvement in $PaCO_2$, MIP, and reduced hospitalization after resting respiratory muscle. Since then various randomized studies have been conducted with selection criteria such as those defined by Rochester and Martin (79): reduced MIP, hypercapnia, low $Pao_2$, dyspnea, and paradoxical motion of the chest wall. One of the major problems is that it seems difficult to obtain electromyographic proof of rest of the diaphragm or accessory muscles during the rest sessions in all subjects without specific training. This was particularly stressed by Rodenstein et al. (90) but minimized by Nava et al. (91). Initial work was performed with "ponchowrap" ventilators and cuirass ventilators used as intermittent negative pressure support (INPV). The duration of application of INPV varied from one hour (92) to 8 hours a day (93).

Some positive results have been reported in small trials, such as an increase in $Pi_{max}$ (94–96) and sustained voluntary hyperventilation (94), in the 12-minute walking distance, in vital capacity, $PaCO_2$, and dyspnea (95,96), and in breathing pattern, with decreases in RR and occlusion pressure and an increase in $V_T$ (95,96). Nasal intermittent positive pressure ventilation (NIPPV) has recently been proven to be successful in acute stages for COPD patients (97). With this in mind, studies have been conducted in order to assess the effect of NIPPV in chronic stages including hypercapnia. Belman et al. (98) compared NIPPV and INPV in COPD patients and concluded that NIPPV was the preferred method for resting the diaphragm; this observation had been confirmed earlier (99) during sleep.

Elliott et al. (100) studied COPD patients with chronic hypercapnia (mean $Pco_2$ = 57) and found after 6 months of nocturnal ventilation a drop in median $Pco_2$ from 70 to 57, unrelated to an increase in MIP but likely related to some mechanical improvement.

In contrast, Strumpf et al. (101) in a crossover study of seven patients with a 3-month period on nasal ventilation at night found no functional benefit except in certain parameters of neuropsychological function.

Large controlled studies are thus necessary in order to assess whether such a costly and constraining domiciliary treatment may reduce the number of hospitalizations for ARF with improvement of the quality of life and have an impact on

survival. A recent review by Hill (102) stressed that only subgroups (e.g., patients with severe nocturnal desaturation) may benefit from nocturnal NIPPV. Regrettably, however, the only large blind randomized study that ventilated patients at night at home with a ponchowrap could no demonstrate any benefit even for subgroups of patients with severe hypercapnia, reduced MIP, and/or underweight (103).

### F. General Muscular Training

Depending on the severity of the disease, general muscular performance improvement may be achieved in various ways from simple walking with supplemental $O_2$ to exercise training on a treadmill or bicycle. Exercise training may be proposed even for patients with hypoxia and hypercapnia (104) over 70 years old (105) and/or with major dyspnea.

As reviewed recently by Ioli et al. (105a), these programs, in most studies, do not improve either lung function tests at rest or respiratory muscle function. This is probably also true for cardiovascular function. On the contrary, the ventilatory regimen is reduced mainly due to the reduction in lactic acidosis (106) when patients are trained above the so-called "anaerobic threshold" (107,108). Beneficial effects on dyspnea (109) and life quality (110) have been observed.

Training has been proposed in order to train arm and thoracic muscles (111,112) with the rationalization that these muscles are more used in severely affected COPD than are leg muscles. Again, studies of the real impact of these techniques on survival and/or progression of the disease are lacking.

Recently Weiner et al. (113) reported a study where respiratory muscle training combined with general exercise conditioning had additional beneficial effects on exercise performance.

## III. Techniques That Could Improve Lung Function In Acute Respiratory Failure in Chronic Obstructive Lung Disease

### A. Airway Clearance

An extensive review supporting the need for chest physiotherapy in the intensive care unit has been provided by Mackenzie (114). IN most quoted papers or personal results, CPT with body positioning and airway clearance including airway suctioning is applied in patients with specific causes of ARF such as atelectasis, pneumonia, and lung contusions. In those patients chest physiotherapy may show very useful results, with improvement in x-ray, gas exchange parameters, and airway and lung mechanics. Supplemental $O_2$ during CPT is recommended in order to avoid transient hypoxia or cardiac arrhythmias, especially with airway suctioning.

The literature concerning COPD patients are ARF, ventilated or not, is generally less positive, although plugs and atelectasis probably need the same approach as in other cases of ARF. Faling (115) summarized some results for COPD with acute exacerbations. Anthonisen et al. (116) showed that chest physiotherapy applied to 36 patients with expansion exercises, postural drainage, and vibrations had no effect on temperature curves, sputum volume, or blood gases as compared to 33 patients treated with conventional therapy.

Campbell et al. (117) showed that postural drainage, percussion, cough, and vibrations induced a significant fall in $FEV_1$ not observed with postural drainage and cough alone. Wollmer et al. (118) published some equivalent results.

Newton and Bevans (119) observed no differences in lung function, blood gases, and hospital stay when compared to conventional treatment alone. Despite an increase in sputum production with CPT and IPPB, Devroey et al. (120), influenced by the work of Zidulka et al. (121) showing that clapping could induce microatelectasis in dogs, studied the effect of chest percussion on gas exchange in six intubated, ventilated COPD patients with multiple inert gas techniques. They observed no change in $Pao_2$ but a slight increse in shunt, suggestive of induced microatelectasis as in dogs.

In general, these studies do not support the need for chest physiotherapy in ARF in COPD. However, there is probably a role for these techniques in patients with evidence of hypoventilation and/or atelectasis due to mucus plugs.

### B. Breathing Pattern and Gas Exchange

Aubier et al. (122) have shown that COPD patients in ARF show a large increase in breathing drive with rapid shallow breathing. Derenne et al. emphasized that the stressed respiratory pump shows hyperinflation with rapid shallow breathing, paradoxical chest wall motions, and increased accessory respiratory muscle and expiratory muscle activity. Electromyographic signs of fatigue have also been documented (86). In such circumstances, trying to change the breathing pattern as for patients in a stable situation is probably impossible and not recommended if we remember that Bellemare and Grassino (44) showed that even in severe stable chronic airway disease an increase in VT and/or TI/TOT put the PTI in the area of the fatigue zone.

Milic-Emili et al. (123) showed that patients in ARF experience a further increase in the work of breathing due to hyperinflation and intrinsic PEEP. With this in mind, applying continuous positive airway pressure (CPAP) may reduce in spontaneously breathing patients the work of breathing (124). Further studies are needed in order to prove that such mechanical help could avoid mechanical ventilation,but some studies have confirmed that CPAP may help therapists wean COPD patients from ventilators (125,126). Ambrosino et al. (127) tried positive support ventilation by nasal mask in severe COPD patients and observed some

interesting changes in the breathing pattern (VT increased; fr decreased) and improvement in gas exchange along with a decrease in diaphragmatic activity.

### C. Body Positioning and Gas Exchange

In normal subjects V/Q distribution has been well studied in various positions (128) leading to the concept that both ventilation and perfusion respect gravity, with preferential regional ventilation and proportionally more perfusion in the dependent area. Furthermore, the decrease of FRC in the supine position puts the tidal volume below the closing capacity and therefore influences V/Q ratio to an extent that measurable changes in $Pao_2$ are possible in elderly and/or obese subjects (129,130). In COPD patients, however, body position–related changes in FRC are rather small (130,131). Only variable and minor changes are observed in $Pao_2$ in the supine (131) and lateral positions (120).

In patients with unilateral consolidation, body position may be of importance in terms of V/Q and $Pao_2$. When the affected lung is the dependent one, the $Pao_2$ may be greatly decreased (132–134) compared to when the good lung is the dependent one. This is probably also true for COPD patients when respiratory failure is explained by unilateral disease, although that concept has been questioned recently by Chang et al. (135).

Thus for acute situations there are no theoretical reasons for imposing a given body position in COPD patients. Probably the one spontaneously chosen by a conscious patient to minimize dyspnea should be respected, even for therapies such as $O_2$ aerosols or pressure support.

## IV. Conclusions

Chest physiotherapy in the management of patients with chronic to acute respiratory failure due to chronic airway obstruction lung disease is probably of importance but needs further evaluation in order to have a solid physiological background. Today, guidelines and unequivocal recommendations are scarce but may include the following:

1. Airway clearance techniques should be restricted to productive ($> 30$ ml/day) patients in the chronic stage and when specific clinical and/or radiological indications appear in the acute stage.
2. The spontaneously adopted breathing pattern both in chronic and acute stages seems to be an appropriate adaptation to the increased drive to breathe and the mechanical constraints of the respiratory pump. Imposed pursed-lips breathing may help some patients.
3. Body positioning of patients in both chronic and acute situations should respect the spontaneously adopted position, giving the patient the least

dyspneic sensation. Both the supine and the sitting forward positions have theoretical advantages over other positions.

4. The concept of chronic fatigue has not been clinically validated, and thus respiratory muscular training should be reevaluated and only applied in patients with very weak respiratory muscles. Chronic hypercapnia is probably not a good parameter for justifying these techniques on a long-term basis.
5. General muscular performance improvement using specific muscular training programs is probably valuable for improving activities in daily life. The impact of such programs on survival and/or the natural history of the disease remains to be determined.

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# 25

# Respiratory Muscle Pharmacotherapy

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## I. Introduction

It is becoming increasingly clear that the respiratory muscles play a paramount role in the development of respiratory failure (1,2). As a consequence, interventions improving respiratory muscle function may be of benefit to patients with overt or pending respiratory failure, while interventions adversely affecting respiratory muscle function are likely to be detrimental to such patients. Several interventions involving the respiratory muscles are possible. Respiratory muscle training is a simple and presumably effective way of improving respiratory muscle function (3–7) and may be administered to patients in hypercapnic respiratory failure (8,9). Respiratory muscle rest through intermittent or nocturnal ventilation constitutes another modality to attempt to improve respiratory muscle function. Its value, however, remains questionable in COPD patients (10), and potentially beneficial effects are not necessarily related to possible effects on the respiratory muscles (11). Respiratory muscle pharmacotherapy also has potential for improving respiratory muscle function.

Interest in this area revived after Aubier et al. (12) demonstrated inotropic effects of theophylline on fresh and fatigued diaphragm in normal subjects. Since that time, active research has been carried out in this area, and the effects of

theophylline on the respiratory muscles have become the center of a lively controversy (13–16). Some undisputed information, however, has also emerged from this research. This chapter will provide an overview of this research and its definite and potential clinical implications, with an emphasis on COPD patients in acute and chronic respiratory failure, the subject of the present book.

## II. Rationale for Respiratory Muscle Pharmacotherapy

The limits of respiratory muscle performance are determined mainly by two variables: the force developed during contraction as a fraction of maximal force (Pbreath/Pmax) and the duration of contraction as a fraction of the duration of the respiratory cycle. The duration of contraction for inspiratory muscles obviously is the duration of inspiration ($T_I$). The fractional duration of inspiration then becomes $T_I/T_{TOT}$ (1,17,18). The product of Pbreath/Pmax and $T_I/T_{TOT}$ is the tension-time product of the inspiratory muscles, TTi. For the diaphragm alone, this tension-time product, TTdi, is the product of transdiaphragmatic pressure, Pdi, developed during breathing as a fraction of maximal transdiaphragmatic pressure, Pdimax, and $T_I/T_{TOT}$. In COPD patients, Pbreath increases due to mechanical impairment, increased airways resistance and decreased lung compliance, and dynamic hyperinflation (19,20). Moreover, Pmax is likely to be reduced due to hyperinflation (21) and generalized muscle weakness (22), to which malnutrition (23), cardiac decompensation (24,25), blood gas disturbances, and steroid treatment (26) may contribute. Similarly, in patients with neuromuscular disease and kyphoscoliosis, Pbreath/Pmax increases primarily due to a decrease in Pmax.

If respiratory impairment progresses or if acute respiratory failure occurs due to additional bronchospasm, respiratory infection, or cardiac decompensation, the respiratory muscles move closer to their fatigue threshold (27). Overt fatigue is usually prevented by concomitant reduction of the duration of inspiration such that the tension-time index TTi remains sufficiently low (28,29). This prevents respiratory muscle fatigue, but it also leads to hypercapnic respiratory failure as tidal volume is inappropriately reduced and alveolar ventilation is decreased (1,30). As a consequence, respiratory muscle fatigue will only be present in a small minority of the patients in respiratory failure, presumably mainly in patients with weaning failure (31). These concepts are schematically represented in Figure 1.

The first aim of pharmacological treatment in these patients will be to reduce airways obstruction and consequent hyperinflation with bronchodilators. Thus, Pbreath will be reduced. The second aim may be to improve respiratory muscle function and, consequently, to increase Pmax. Both will interact to produce a reduction in the ratio Pbreath/Pmax, which will move the respiratory muscles away from their fatigue threshold such that a longer duration of inspiration and,

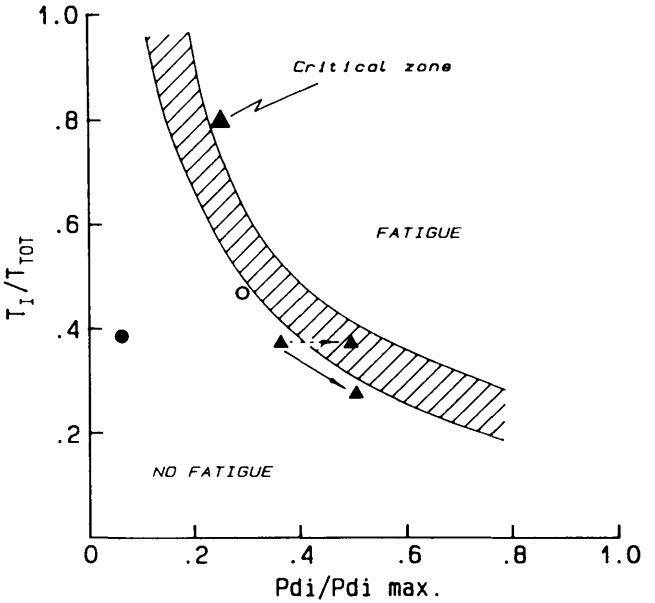



**Figure 1** Relationship between $T_I/T_{TOT}$ and $Pdi/Pdi_{max}$ governing the development of diaphragmatic fatigue. Hatched area represents the critical zone in which fatigue starts to develop. Combinations falling below the hatched area represent breathing patterns that do not cause muscle fatigue, while combinations falling above the area cause diaphragm fatigue. Closed circle = normal adult; open circle = newborn; triangle = COPD patient. With progressing mechanical impairment during acute respiratory failure, the COPD patient needs to increase Pdi and, therefore, might fall into the fatiguing zone (dashed arrow). This is usually avoided by concomitant reduction of duration of inspiration, $T_I/T_{TOT}$ (solid arrow). With drugs improving respiratory muscle force-generating capacity, movement occurs in the opposite direction, thus preventing the occurrence of respiratory muscle fatigue. (Adapted from Ref. 17.)

hence, a greater tidal volume becomes possible (Fig. 1). This in turn will allow a greater alveolar ventilation and thus a lower $Paco_2$.

Three general remarks are of some significance here. Although Pmax is classically used in the sense of maximal tetanic tension, this is not necessarily the case in the reasoning developed above. In any event, inotropic agents do not affect maximal tetanic tension (16), but the reasoning developed above remains applicable when maximal tension at submaximal stimulation frequencies is meant. The latter is indeed increased by inotropic agents (16). In this chapter, the term inotropic agent will be used to mean an agent increasing tetanic tension at submaximal stimulation frequencies.

Second, Pmax may be affected by a number of mechanisms, which include effects on the respiratory muscle cell itself, effects on respiratory muscle substrate supply, and effects on respiratory muscle substrate and energy utilization. These effects will be discussed with the individual inotropic agents. It should be emphasized, however, that in the reasoning developed above, the dimension of muscle energy and oxygen demands is lacking. It is intuitively clear that an agent improving Pmax will not necessarily have a beneficial effect in a clinical setting if this increase in Pmax was achieved at the expense of an inappropriately high increase in muscle energy and oxygen demands, which may in fact compromise the muscle's endurance capacity and promote fatigability. This aspect in general has received little attention (15), although it is of obvious importance for muscles that have to contract continuously as the respiratory muscles do.

Finally, although we are fully convinced of the need for animal models and mechanistic studies, a drug is prescribed to patients in general or in a particular circumstance because a clinical study has demonstrated an effect of the drug on outcome variables in a randomized controlled way. Unfortunately, for most drugs such studies have been incompletely performed. We will first outline some characteristics of respiratory muscle contraction, then we will address drugs with the potential to improve respiratory muscle function, and finally we will deal with drugs that negatively affect respiratory muscle function.

## III. Characteristics of Respiratory Muscle Contraction

Among the group of skeletal muscles, the diaphragm exhibits some unique features. It must contract phasically during life, a function more similar to that of the myocardium than that of the limb muscles. In view of this functional similarity between the heart and the diaphragm, some similarities in their cellular contractile mechanisms, either in the excitation–contraction coupling processes or in their energy supply mechanisms, are expected. The following description will focus on the diaphragm since virtually no studies have been made of the other inspiratory muscles.

### A. Excitation–Contraction Coupling

Evidence is present of some similarity between the diaphragm and the myocardium. Indeed, although the central role of calcium in the excitation–contraction coupling of skeletal muscle is well established, the cellular mechanisms by which calcium is made available to the contractile proteins during excitation remain unclear. It is generally thought that the activation of the contractile elements is essentially independent of extracellular calcium (32). The $Ca^{2+}$ fluxes in skeletal muscle during excitation–contraction coupling are thus regarded strictly as intra-

cellular and independent of extracellular calcium. By way of contrast, in cardiac muscle the passage of calcium across the cell membrane is of major importance.

In vitro studies (33) have challenged these classical concepts. It was demonstrated that in calcium-free medium, isolated rat diaphragmatic fibers behaved similarly to single papillary muscle fibers. Indeed, a striking similarity was observed between their contractile responses to extracellular calcium deprivation: in both cases it resulted in complete twitch abolition. By way of contrast, no twitch abolition was observed with single soleus or extensor digitorium longus fibers, a slow and fast peripheral skeletal muscle, in calcium-free medium. These data have been confirmed in dogs in vivo (34) when the animals were rendered hypocalcemic by infusion of a $Ca^{2+}$ chelator, which led to a decrease in ionized extracellular calcium. Under these conditions a marked depression in diaphragmatic force–generating capacity was noted, whereas the sartorius, a peripheral skeletal muscle of similar histochemical profile, was not affected. Therefore, it appears that the diaphragm may be a unique skeletal muscle that resembles cardiac muscle. These results may provide new insight into the mechanisms of diaphragmatic contraction, notably by underlining its characteristics compared to other striated skeletal muscle. They may have important pharmacological implications: consequent to the similarity between diaphragmatic and cardiac muscle fiber's dependence on extracellular $Ca^{2+}$, it is conceivable that drugs or agents that exert a direct positive or negative inotropic effect on the myocardium may have similar actions on the diaphragm.

### B. Energy Supply

Respiratory muscle dysfunction is also expected to occur when the supply of nutrients to the respiratory muscles is insufficient to meet the metabolic demands (35). During breathing, the oxygen requirements of the respiratory muscles, especially the diaphragm, are primarily met by increased diaphragmatic blood flow (36) during unobstructed hyperventilation (37), hypoxia, and exercise (38). It appears possible that when blood flow to the muscle is insufficient, lack of oxygen leads to a shift towards anaerobic glycolytic pathways of high-energy phosphate generation. This shift is expected to increase the acid accumulation associated with a given level of ATP turnover, impairing sarcoplasmatic reticulum function and reducing the force-generating capacity of the diaphragm.

Moreover, blood flow may play a role in "washing out" of the by-products of cellular metabolism (39,40). Thus, it is possible that increased diaphragmatic blood flow may increase the washout of toxic by-products of cellular metabolism in addition to improving diaphragmatic energetics.

Energy supply to the diaphragmatic muscle cells not only depends upon global diaphragmatic blood flow but also upon its distribution at the microcircula-

tory level. Recently, it has been shown in an experimental rat model in vivo that the microcirculatory network was also different from peripheral skeletal muscle (41). Indeed, the capillary density appears to be much higher in the diaphragm than in the peripheral muscles. Again the capillary density in the diaphragm was close to the myocardium. Furthermore, the control of diaphragmatic microcirculation appears to be different from peripheral muscle as well. The endothelium-dependent relaxation elicited in the diaphragmatic arterioles by acetylcholine is mediated by both prostaglandins and nitric monoxide, whereas it is mediated only by nitric monoxide in the peripheral muscle (42).

Pursuant to the above-mentioned characteristics of the diaphragm, diaphragmatic function can be pharmacologically modulated at different levels, including the excitation–contraction coupling process and the energy supply to the muscles. By antagonizing humoral mediators like prostaglandins, some pharmacological agents may be beneficial, whereas some others may be detrimental. We will review first drugs with a positive effect and then those with a negative effect.

## IV. Drugs That Improve Respiratory Muscle Function

Many drugs have been claimed to improve respiratory muscle function. Some of these remain controversial, at least in their effect on the respiratory muscles, mainly because in clinical studies it is often difficult to separate the effect on respiratory muscle contractility from other effects, such as bronchodilating or central stimulating effects. For each of these compounds, we will briefly review the evidence available before we attempt to come to an integrative view. We will emphasize the clinical data, and data obtained in animals or in isolated tissue studies will not be reviewed in great detail.

### A. Methylxanthines

Methylxanthines constitute a class of compounds in clinical practice most classically used as bronchodilators. Theophylline is the most widely used of these compounds. The effects of theophylline on respiratory muscle function have been the center of a lively controversy, with some investigators obtaining positive results (12,43) while others fiercely debate these results, having obtained negative findings (13,14,44). Similarly, animal models studying the effects of low, potentially in vivo attainable serum levels have yielded negative (16,45,46) as well as positive results (47–51). There is no doubt that theophylline exerts inotropic effects on the diaphragm at very high supratherapeutic concentrations (1–2 mM) (50,52). These inotropic effects may be related to four different mechanisms.

First, they may be caused by enhanced transmembrane $Ca^{2+}$ flux, as in dogs the effect was blocked by verapamil, a blocker of the voltage-operated $Ca^{2+}$

channels (34). Second, they may be related to hyperpolarization of the cell membrane (53). Third, they may be related to enhanced $Ca^{2+}$ release by the sarcoplasmic reticulum, as was demonstrated for caffeine (54). Finally, they may be related to adenosine receptor blockade, an effect shown to occur at low concentrations (55,56). Adenosine, however, did not exert any effects on diaphragmatic force–generating capacity in vitro (57).

The present chapter will not attempt to reopen the above-mentioned debate. We will outline five recently developed lines of research that may be clinically significant to COPD patients in acute or chronic respiratory failure. First, we demonstrated in supine anesthetized dogs that aminophylline administration promoted recruitment of expiratory muscles in a dose-dependent way (58). This expiratory muscle recruitment could have a number of consequences if present in patients. It could relieve the inspiratory muscles by taking up part of the work of breathing. This should reduce the sensation of dyspnea and prevent inspiratory muscle failure. To the extent, however, that expiratory flow limitation is present in patients with respiratory failure, the unloading of the inspiratory muscles may be minimal. Expiratory muscle recruitment may still move the diaphragm to a more favorable position on its length-tension curve and alter diaphragm geometry, both of which could improve the diaphragm's effectiveness as a pressure generator.

Second, we recently observed that the inotropic effects of theophylline were enhanced by foreshortening (59,60). Indeed, both in vitro (59) and in vivo (60), the inotropic effects on canine diaphragm were clearly greater at 70% optimal length than at optimal length, Lo. The difference was important, about three- to fivefold, and at 70% Lo inotropic effects were obtained at serum levels that could be reached in patients (Fig. 2). Since hyperinflation and consequent diaphragmatic shortening are likely to be present in patients with acute respiratory failure, the effects of theophylline in these patients may be clearly different from the effects of theophylline in patients without hyperinflation. This effect on foreshortened diaphragm is likely to be related to restoration of T-tubular function, which is impaired at shorter diaphragm length (61), an action that has been clearly demonstrated for caffeine (62,63). Indeed, these authors demonstrated that with muscle shortening the activation of the central myofibrils was inhibited, while the activation of the peripheral myofibrils appeared normal, presumably due to inadequate inward spread of the action potential through the T-tubular system. Caffeine was shown to restore the activation of the central myofibrils. Whether such an effect would also be present in chronically foreshortened muscle in which sarcomere adaptation is present (64–66) remains unclear. Studies specifically addressing the inotropic effects of theophylline in patients with acute or chronic hyperinflation still remain to be performed. It is not excluded that the degree of hyperinflation may explain some of the discrepant findings previously observed.

Third, studies performed in patients with chronic poorly reversible airflow limitation on average have consistently shown improvements in pulmonary func-

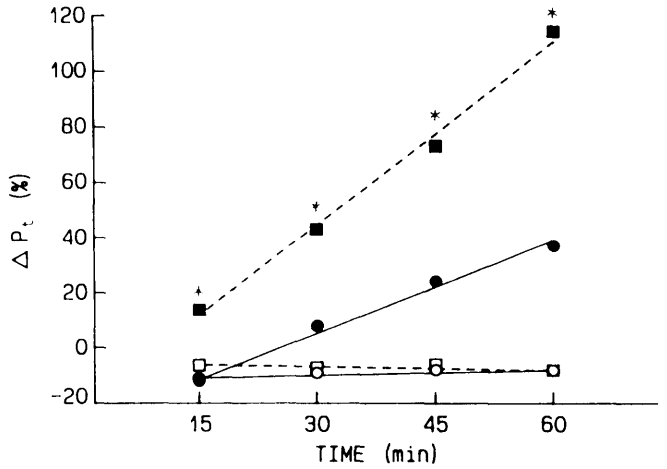



**Figure 2** Increase in twitch tension (ΔPt) in canine diaphragm in vitro vs. time (minutes). Each data point corresponds to 15-minute incubation with an increasing theophylline concentration (20, 100, 200, 400 mg/liter). Circles = bundles placed at Lo; squares = bundles placed at 70% Lo. Closed symbols = bundles treated with theophylline; open symbols = control bundles treated with additional Krebs solution at the same points in time. Increase is expressed as a percentage of control twitch tension. (From Ref. 59.)

tion (67–70). Evidence that these improvements are due to improved respiratory muscle function, however, is tenuous at best. Although improvement in respiratory muscle function was clearly demonstrated in two studies it remains impossible to determine whether it results from a direct effect on the respiratory muscles or is caused by the bronchodilatation induced by theophylline.

Fourth, in one study beneficial effects were obtained in patients with neurological disease (71). Whether the effects of theophylline on diseased muscle might be different from the effects on healthy muscle has received remarkably little attention so far, although it is of considerable relevance to patients with neuromuscular disease.

Finally, in recent studies (72) we examined the effects of low-dose theophylline administration (40 mg/kg, resulting in a serum level of about 20 mg/kg after distribution phase) on diaphragmatic oxygen consumption during quiet breathing and inspiratory resistive loading in dogs. We observed that theophylline increased diaphragmatic oxygen consumption at any given diaphragmatic tension time index (TTdi), suggesting that theophylline might increase oxygen consumption for a given amount of work performed (Fig. 3). This suggests that potential inotropic effects are not necessarily beneficial if associated with reduced endurance. In vitro experiments suggest that this might be the case, since it was

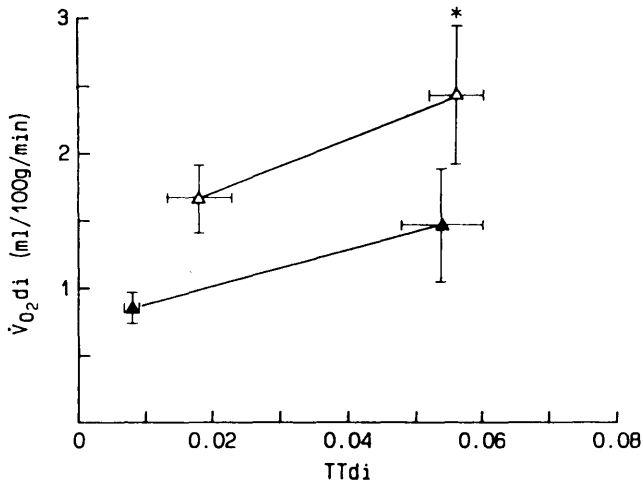



**Figure 3** Diaphragmatic oxygen consumption $\dot{V}o_2di$ expressed in ml/100 g tissue/min vs. diaphragmatic tension-time index, TTdi. Open triangles = data after theophylline administration; closed triangles = control. Means ± SD. $*p < 0.05$. (From Ref. 72.)

repeatedly observed that theophylline-treated muscle bundles fatigued faster than control bundles (16,45).

### B. Selective $\beta_2$-Agonists

This class of drugs has also received considerable attention. Evidence is available that some $\beta_2$-agonists improve force output of fatigued canine diaphragm (46,73, 74), while in general no effect or only a very small effect is seen with fresh canine diaphragm (73). In contrast, salbutamol produced such effects to a much smaller extent in dogs (46,75) and humans (76). It should be stressed that the obtained effects in dogs are effects on long-lasting diaphragmatic fatigue, and it is at present unclear under what circumstances such fatigue is present in patients (77).

Along these lines, one clinical trial conducted in COPD patients did not demonstrate any beneficial effects on the diaphragm (78). It should be emphasized, however, that this study was performed essentially on normocapnic patients, and that general belief would indicate that diaphragm fatigue is unlikely to be present in these patients. A controlled randomized study on the effects of systematically administered $\beta_2$-agonists in patients with either chronic or acute hypercapnic respiratory failure would seem warranted.

If $\beta_2$-agonists improve muscle performance, several mechanisms may be involved. By interaction with the $\beta_2$-receptor, cAMP is increased, which in turn influences a number of cellular processes that may enhance contractility, includ-

ing enhanced $Ca^{2+}$ reuptake by the sarcoplasmic reticulum (making more $Ca^{2+}$ available for subsequent release), activation of phosphorylase, or stimulation of $Na^+$-$K^+$ exchange at the sarcolemma. An effect on the neuromuscular junction may be present, and the drugs are also expected to enhance diaphragmatic blood flow. Recent experiments demonstrated that diaphragmatic blood flow was increased much more after treatment with broxaterol than with salbutamol (79). Enhancement of diaphragmatic blood flow is a likely mechanism for the observed effect on fatigued canine diaphragm. Since this action was found to be clearly smaller with salbutamol, one would expect the effect of salbutamol on the recovery of low-frequency fatigue to be smaller as well. This was in fact observed (80). It remains unclear why these different $\beta_2$-agonists have profoundly different effects on diaphragmatic blood flow.

### C. Dopamine

Under certain circumstances improvement of respiratory muscle blood flow improves the muscles' force-generating capacity. This is the case for mechanical hyperperfusion of fatigued diaphragm and is believed to result from wash-out of metabolites (40). Whether improvement of blood supply to fresh muscle also improves the force-generating capacity is not known. An elegant study by Aubier et al. (81) demonstrated that in patients in acute respiratory failure being ventilated mechanically, dopamine infusion increased diaphragm blood flow and the Pdi generated during phrenic nerve stimulation (Fig. 4). These variables returned to baseline after dopamine infusion. These data appear promising, but before it can become a widely spread clinical practice to treat patients with respiratory failure with dopamine, a randomized controlled clinical trial addressing the effects of dopamine on outcome variables in patients with acute or chronic respiratory failure is required. At present and intuitively, dopamine would be expected to produce beneficial effects in patients in whom the diaphragm is either fatigued or at least operating at a workload at which it is critically dependent upon its substrate delivery. It is difficult to distinguish such patients from other patients with respiratory failure, and therefore with our present state of knowledge it may be difficult to identify potential candidates for treatment with dopamine.

### D. Phosphodiesterase Inhibitors

New and much more powerful phosphodiesterase inhibitors have been developed recently (82). These include amrinone, milrinone, enoximone, and piroximone (82–85). Some of these drugs are clinically used as cardiac inotropic agents in patients with cardiac failure or after cardiac surgery. Few studies have been conducted to assess the effects of these drugs on the respiratory muscles. One study demonstrated that milrinone enhanced force production in rat diaphragm in

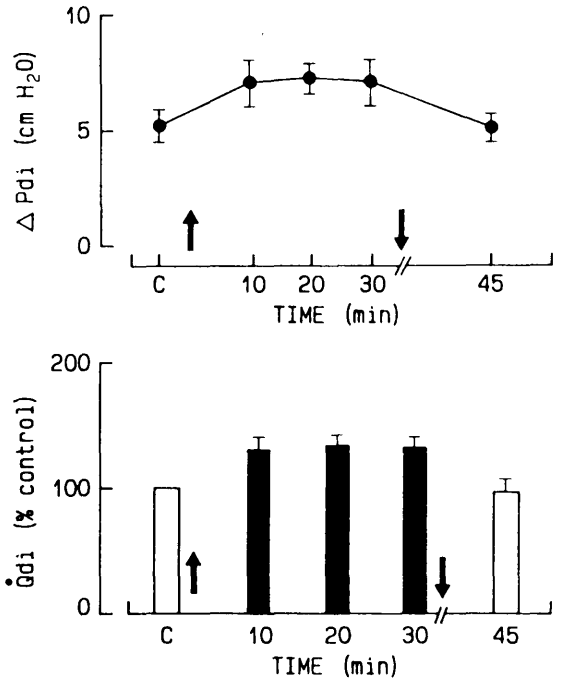



**Figure 4** Upper panel: Change in Pdi generated during phrenic nerve stimulation under control conditions throughout infusion of dopamine and 15 minutes after the end of dopamine administration in eight patients. The first arrow shows the start of the infusion, the second arrow the end of the infusion. Lower panel: Diaphragmatic blood flow $\dot{Q}di$, measured with the phrenic vein drop count method, under control conditions (open bars) and during infusion of dopamine (closed bars) in three patients. First arrow shows start of infusion, second arrow end of infusion. Diaphragmatic blood flow is expressed as a percentage of control. Bars ± SE. (From Ref. 81.)

vitro at submaximal stimulation frequencies and voltages. The effect was independent of transmembrane $Ca^{2+}$ flux and metabolites of the arachidonic pathway metabolism (86). Inotropic effects are expected to result from phosphodiesterase inhibition and consequent increase in cAMP content and its subsequent effects on cellular physiology. They were, however, achieved at very high concentrations likely to exceed the serum levels obtained in patients by factors. Another study (87) demonstrated that amrinone enhanced diaphragm blood flow in an isolated strip preparation for a given force developed during stimulation. This effect was obtained at the recommended dosage.

None of these drugs, however, has been critically tested in clinical studies

as an inotropic agent for the respiratory muscles. Until this has been done, the value of these drugs remains questionable in COPD patients with acute or chronic respiratory failure.

### E. Cardiac Glycosides

These drugs have been known as inotropic agents for the heart since antiquity. They remain well-established drugs in the treatment of cardiac failure and arrhythmia. Recently, digoxin has also been studied as an inotropic agent on the diaphragm. Aubier et al. (88) studied the effects of digoxin on diaphragmatic contractility in dogs and found that Pdi increased by 20–25% at therapeutic doses. In another study, Kikuchi et al. (89) demonstrated that treatment with deslanoside delayed the onset of diaphragmatic fatigue in dogs. In contrast, Sherman et al. (90) could not demonstrate an inotropic effect of digoxin on rat or guinea pig diaphragm.

Aubier et al. (91) demonstrated an effect of digoxin in COPD patients during acute respiratory failure. Twitch Pdi increased by almost 20% at therapeutic digoxin levels, an effect that could not be explained by an increase in cardiac output, which was absent (Fig. 5). This inotropic effect is likely related to inhibition of the $Na^+,K^+$–ATP-ase, since ouabain also increased Pdi in animal studies. The balance of the animal studies and the single study in patients at present appear reasonably positive for digoxin, and the time has come to study the effects of digoxin administration on outcome variables in COPD patients with acute and chronic respiratory failure.

### F. Antioxidants

A number of studies have indicated that diaphragmatic contractions induce the formation of oxygen free radicals (92,93). In addition, Nashawati et al. (94) demonstrated that infusion of free radical–generating solution in the canine diaphragm reduced twitch tension, whereas diaphragm blood flow remained unaltered. This suggests that free radical–mediated diaphragmatic injury can result in decreases in diaphragm contractility. Moreover, administration of the free radical scavenger *N*-acetylcysteine was shown to attenuate the rate of development of diaphragm fatigue in rabbits (95). The diaphragm dysfunction during endotoxemia may also be related to oxygen free radical production and may be prevented by *N*-acetylcysteine administration (96). These observations are all very interesting and may prove to be important in either preventing or treating diaphragm dysfunction in a number of situations relevant to clinical medicine, such as reperfusion injury, fatigue, eccentric contractions, and hypothyroidism (97).

In this context, however, it is at this point in time difficult to predict what these observations mean for the pathogenesis and treatment of acute and chronic

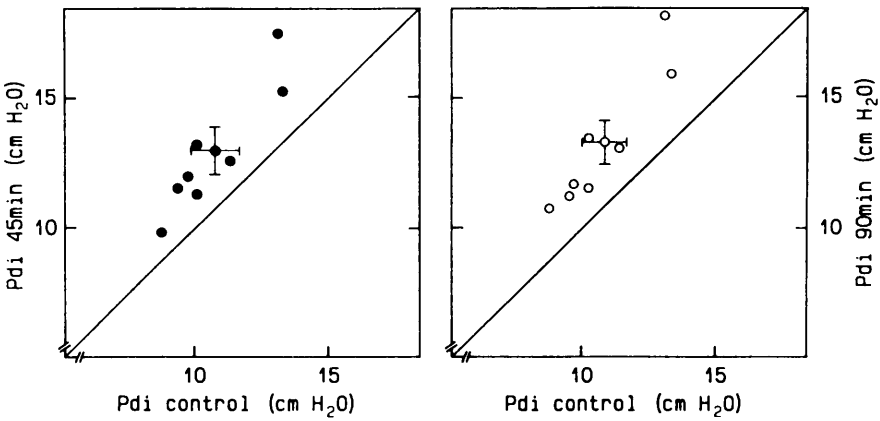



**Figure 5** Identity plot of individual and mean twitch Pdi ($cmH_2O$) obtained during phrenic nerve stimulation in eight patients before (control) and 45 minutes after (left), and 90 minutes after (right) digoxin administration. Closed circles are data obtained after 45 minutes, open circles after 90 minutes. (From Ref. 91.)

respiratory failure, nor is it currently possible to determine the role of free radical scavengers in the treatment of these conditions. Clinical studies on the effects of treatment with oxygen free radical scavengers on outcome variables in these patients may provide a conceptual breakthrough.

### G. Cyclooxygenase Inhibitors

The role of prostaglandins and particularly $PGE_2$ in the genesis of skeletal muscle dysfunction has been established (98). The role of $PGE_2$ in diaphragmatic dysfunction induced by *Escherichia coli* administration was indirectly demonstrated in the rat (99). Indeed, in the latter work, the administration of indomethacin, an inhibitor of cyclooxygenase, completely inhibited the diaphragmatic dysfunction consecutive to *E. coli* administration. As stated for the oxygen free radicals, however, the clinical relevance of these observations remains to be established.

### H. Anabolic Steroids

In view of the frequent reports of catabolic effects of glucocorticosteroids on muscles, it appears reasonable to attempt to improve respiratory muscle function with anabolic steroids. Preliminary studies in rats indicate that cortisone-induced muscle atrophy may be partly prevented by treatment with anabolic steroids (100). Treatment with anabolic steroids may further result in increases in respiratory muscle mass in normal rats (101). These effects, however, appear to be small.

Studies critically assessing their use in patients with respiratory failure are not yet available.

## V. Drugs That Negatively Affect Respiratory Muscle Function

It has been known for a long time that some drugs produce negative effects on peripheral muscles, but effects on respiratory muscles have generally only recently been described. Also, electrolyte disturbances may affect respiratory muscle function. Knowledge of these effects provides us with another approach to respiratory muscle pharamcotherapy. Indeed, cessation of this treatment or correction of these electrolyte disturbances will improve respiratory muscle function. In general, and with our present state of knowledge, this form of respiratory muscle pharmacotherapy is of more obvious clinical significance than that of the inotropic agents available so far and their effects as thus far demonstrated.

### A. Corticosteroids

Corticosteroids have been known to produce muscle weakness since the original observations made by Cushing (102). Their effects on the respiratory muscles have only recently been studied. We will discuss observations in animal models as well as observations made in patients.

#### *Animal Studies*

Several animal models of steroid-induced myopathy have been developed (103–110). All of these studies indicated that the diaphragm was involved in steroid-induced myopathy and that in these animals alterations in contractile properties (103–106), histological and histochemical properties (103,108,109), and biochemistry (103,107,109) were present after treatment with corticosteroids. Changes did not, however, follow a uniform pattern. Moore et al. (104) found contractile properties to be essentially unchanged when corrected for the loss in muscle mass caused by muscle atrophy. Wilcox et al. (103) observed prolongation of half-relaxation time and time to peak tension and augmentation of force development at low stimulation frequencies, while others found no alterations in contraction time or even reductions in half-relaxation time (105) and in maximal tetanic tension (105,106). Histochemically atrophy of either type IIb fibers (103) or all fiber types (108) was observed.

At present no clear-cut explanation for these discrepant findings is known. Obvious potential determinants are interspecies differences, differences in dose and type of preparation used, differences in the route of administration, and concomitant malnutrition (111,112). Recently, Dekhuijzen et al. (110) pointed to

the difference between fluorinated and nonfluorinated steroids and to the potential significance of the dose of steroid administered. Indeed, they demonstrated that treatment with triamcinolone, a fluorinated steroid, produced atrophy of type IIb fibers with consequent changes in diaphragmatic contractile properties, while prednisolone, a nonfluorinated steroid, caused more subtle myogenic changes without type IIb fiber atrophy (Fig. 6). In contrast to most of the studies mentioned above, they used more realistic doses of steroids likely to produce chronic steroid-induced myopathy instead of acute myopathy (see below). The fact that in many of the above studies very high doses of steroids were used may be in part responsible for the discrepant findings (113). More study is needed to clarify these issues. Clarification would be useful because a good understanding of the alterations in diaphragm and peripheral muscle function caused by steroids would allow us to distinguish these from other causes of muscle weakness often present in patients (21). Moreover, if the exact mechanism whereby steroids affect respiratory muscle function were known, being able to reverse these effects with antagonists would become considerably more likely. Such antagonists might include growth hormone or insulinlike growth factor 1 (IGF-1).

### *Human Studies*

Three types of studies have been made of the effects of steroids on respiratory muscle function in normal subjects and patients: those in which steroid treatment is administered to normal subjects, occasional observations on patients developing steroid-induced myopathy, and studies in patients in whom the relationship between respiratory and peripheral muscle weakness and steroid treatment is analyzed.

The effects of treatment with prednisone 20 mg/day for 2 weeks were studied by Wang et al. in normal subjects (114). No effects on PImax, PEmax, $Pdi_{max}$, or respiratory muscle endurance were observed. It should be stressed, however, that the dose was relatively low, duration of treatment was short, and that no other causes of muscle weakness such as malnutrition (23) or cardiac decompensation (24,25) were present. Although not demonstrated directly it appears reasonable that these factors could enhance patient susceptibility to the detrimental effects of steroids in patients. This speculation needs further testing.

Several case reports have been made on patients developing steroid-induced myopathy. Two distinct clinical patterns have been described. Patients being treated with massive doses of steroids (hydrocortisone 1–4 g/day, dexamethasone 40 mg/day) may develop acute myopathy (115–119). This clinical entity is characterized by generalized muscle weakness, affecting proximal as well as distal muscles, muscle necrosis affecting all fiber types and rhabdomyolysis (116,118), and massive elevation of serum creatine phosphokinase levels. Recovery may take more than 6 months (118). This pattern was suspected to occur in 19

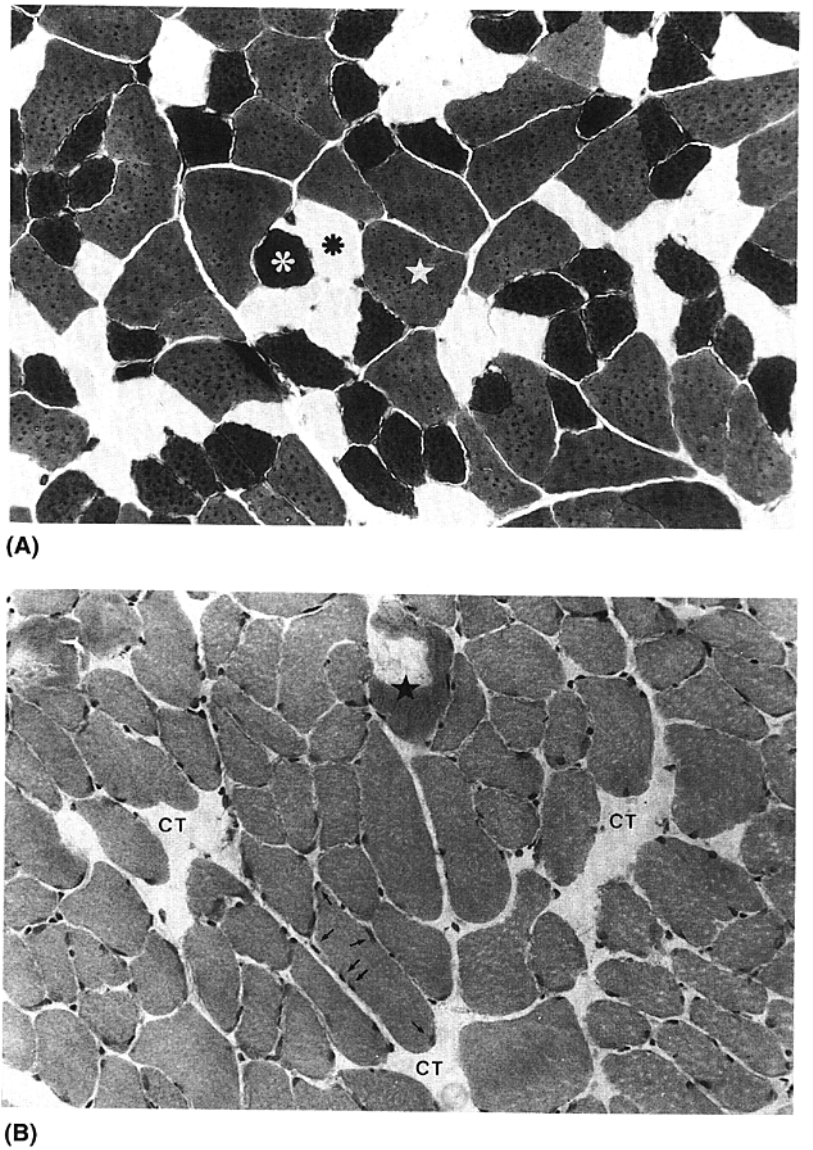
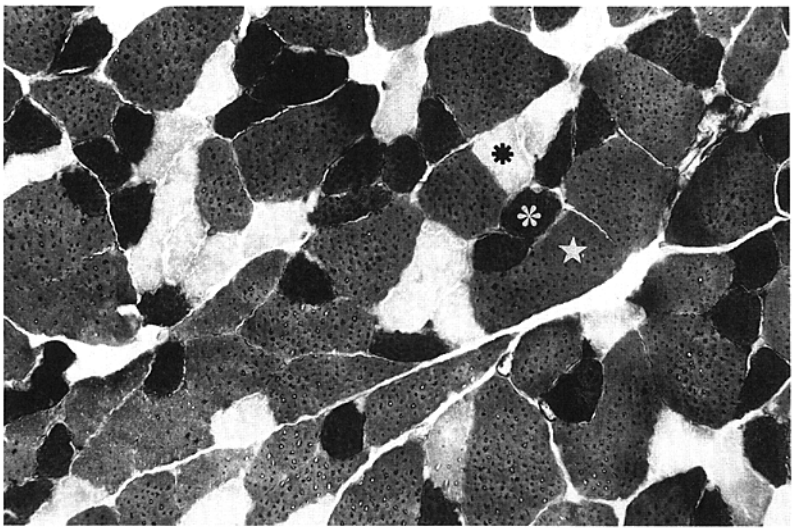
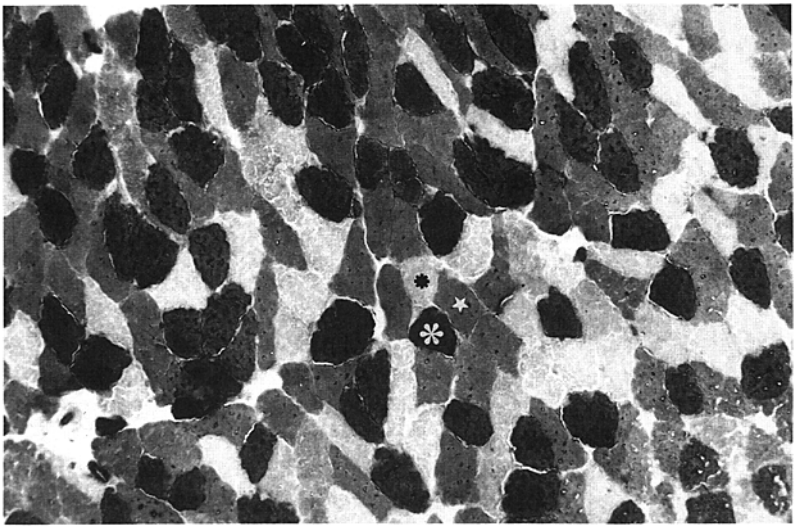



**Figure 6** (A) ATP-ase staining of normal rat diaphragm at pH 4.3. Type I fiber = ✻; Type IIa fiber = ✻; Type IIb fiber = ★. (B) ATP-ase staining of rat diaphragm at pH 4.3 coming from rats treated with a low-dose prednisolone (1.25 mg/kg/day) for 4 weeks. Same pattern as normal rat diaphragm. (C) H&E stain of rat diaphragm coming from rats treated with a high dose of prednisolone (5 mg/kg/day) for 4 weeks. Note increased amount of connective



(C)



(D)

tissue in between muscle fibers (CT), increased number of nuclei (arrows), and scattered necrotic fibers (★). (D) ATP-ase staining of rat diaphragm at pH 4.3 coming from rats treated with triamcinolone (1 mg/kg/day) for 4 weeks. Same symbols as in upper panels. Note severe Type IIb fiber atrophy. (From Ref. 110.)

out of 25 patients treated with very high doses of steroids for status asthmaticus (119). Concomitant treatment with vencuronium appeared to be a potential risk factor (119).

Chronic myopathy develops in patients treated with moderately high doses of steroids (prednisone 40 mg/day) during several weeks or months. It is characterized by proximal muscle weakness, normal muscle enzymes, and vastly elevated creatine excretion in 24-hour urine (120). Reversible respiratory muscle involvement was demonstrated in patients with systemic disease (121) and asthma and COPD (26) (Fig. 7). The changes in muscle pathology with chronic steroid-induced myopathy have not been systematically and critically analyzed.

Three studies have analyzed the relationship between muscle weakness and steroid treatment in patients with asthma and COPD. Bowyer et al. (122) only found clear muscle weakness in patients being treated with more than 40 mg prednisone/day, although the relationship between muscle weakness and steroid dose as continuous variables was not analyzed. Picado et al. (123) found no reduction in PImax and PEmax in outpatients being treated with an average daily dose of 12 mg prednisone, and the diameter of type IIb fibers was found to correlate with nutritional status rather than with steroid treatment. By way of contrast, Decramer et al. (124) observed that quadriceps force and PImax were significantly related to steroid dose in patients being treated with repetitive bursts of steroid therapy. This relationship was independent of the degree of airflow obstruction. The average dose was only about 5 mg prednisone/day. There is no firm explanation for the apparent discrepancy between the latter study and the former two studies. A potential explanation may be that repetitive bursts of steroid treatment produce myopathy more readily than continuous treatment with low doses. This needs to be analyzed in a prospective clinical trial.

### B. Other Drugs

Other drugs have been described to produce neuropathy, neuromuscular blockade, or myopathy. Some drugs may affect nerves, muscle, and neuromuscular junction simultaneously. These drugs were recently included in an excellent review (125). Drugs producing myopathy may be divided into those that produce destructive lesions in muscle and those affecting the normal mechanism of muscle contraction (126). Drugs producing destructive lesions in muscle include clofibrate, alcohol, heroin, cimetidine, chloroquine, aminoglycosides, D-penicillamine, and propanolol. Drugs affecting the normal mechanism of muscle contraction include those producing hypokalemia, such as diuretics. Whether and to what extent these drugs affect the respiratory muscles has not systematically been studied.

### C. Electrolyte Disturbances

Several electrolyte disturbances have been shown to produce respiratory muscle weakness. Correction of these electrolyte disturbances is of obvious clinical

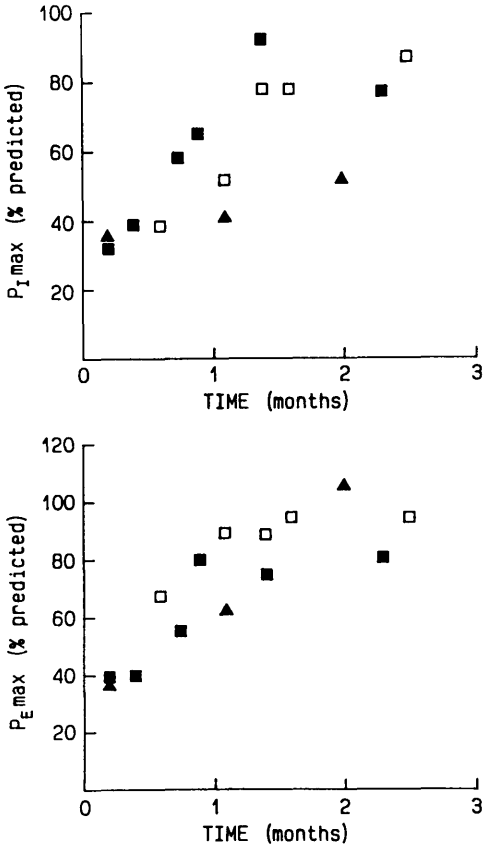



**Figure 7** Upper panel: Recovery of $P_I$max (% predicted) in three patients with chronic airflow limitation (■, □, ▲) and steroid-induced myopathy after cessation of steroid treatment, versus time (months). Lower panel: Recovery of $P_E$max (% predicted) in the same three patients after cessation of steroid treatment versus time (months). (Modified from Ref. 26.)

importance in patients in respiratory failure. Respiratory acidosis was shown to depress diaphragmatic function in dogs (127) and in normal human beings (128). In the latter study a $Paco_2$ of 54 mmHg was shown to depress contractility and endurance time of the diaphragm. Metabolic acidosis also may curtail diaphragmatic function in dogs (129). Hypophosphatemia was shown to depress diaphragmatic function in patients being ventilated for acute respiratory failure. Correction of serum phosphorus was accompanied by a marked increase in twitch transdiaphragmatic pressure (130). A representative example is shown in Figure 8. Although the effects of many other electrolyte disturbances on respiratory muscle

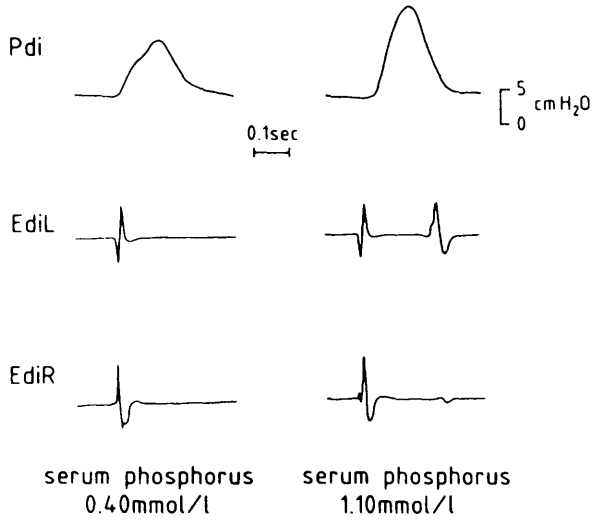



**Figure 8** Representative tracing of Pdi and electrical activity of left hemidiaphragm (EdiL) and right hemidiaphragm (EdiR), during bilateral phrenic nerve stimulation in one patient before and after correction of hypophosphatemia. Note the clear increase in Pdi after correction of hypophophatemia, while the electrical activity during stimulation remained unchanged. (From Ref. 130.)

function such as hypomagnesemia and hypocalcemia have not always been directly demonstrated, correcting all existent electrolyte disturbances appears to be a reasonable approach to patients with acute respiratory failure, chronic respiratory failure, or weaning failure.

## VI. Conclusion

Several substances have been claimed to produce inotropic effects on the respiratory muscles. These include theophylline, $\beta_2$-agonists, dopamine, phosphodiesterase inhibitors, cardiac glycosides, antioxidants, and anabolic steroids. Although active research has been conducted into drugs improving respiratory muscle function for about 10 years, none of the compounds has been unequivocally shown to improve respiratory muscle function in a large fraction of COPD patients with acute or chronic respiratory failure to a clinically significant extent. Some drugs, however, appear very promising in animal models. Properly conducted clinical trials may contribute considerably to the development of this field in the future. It is clear that several drugs may adversely affect respiratory muscle

function, among which glucocorticosteroids have received considerable attention. Steroid-induced muscle weakness is likely to be important in pulmonary patients treated with high doses of corticosteroids, and respiratory muscle weakness may contribute to the development of symptoms and respiratory failure. Recognition of this clinical pattern is important because increased complaints in practice very often erroneously lead to intensification of steroid treatment. Whether treatment with low doses also produces muscle weakness remains questionable. Research is being conducted into substances specifically counteracting the effect of steroids on muscle.

## Acknowledgments

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# 26

# Noninvasive Ventilation

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## I. Introduction

In the field of home mechanical ventilation, noninvasive ventilation has gained wide acceptance (1–3). Noninvasive ventilation can be used as an early treatment to prevent further deterioration of chronic respiratory insufficiency or as an alternative to tracheotomy. Until recently, clinical experience in the acute care setting was more restricted, employing two different approaches. The first approach treats acute decompensation of chronic respiratory insufficiency using the techniques employed for home mechanical ventilation, while the second adapts the equipment used in intensive care units (ICUs) for intubated patients to noninvasive ventilatory support of patients with respiratory distress (4–6). Although very promising results have been obtained with both approaches, we will see that the type of equipment used (e.g., patient-ventilator interface, ventilatory mode, mechanical ventilator) influences the success rate of such techniques. In this chapter we will focus on the techniques used for acute exacerbation of chronic obstructive pulmonary disease (COPD).

## II. Goals of Noninvasive Ventilation During Acute Respiratory Failure

The overall principle of noninvasive ventilation is to deliver adequate ventilatory support without the need to perform endotracheal intubation. In fact, different goals exist behind this principle.

### A. Avoiding Complications of Endotracheal Intubation

Mechanical ventilation is one of the life-saving procedures most widely used in the ICU. However, this technique is accompanied by complications that carry their own morbidity and mortality (7). Because many of these complications are directly or indirectly related to endotracheal intubation or tracheotomy, delivering ventilatory support noninvasively has been a major interest. Complications include those directly related to the intubation procedure, such as cardiac arrest during the procedure, inhalation, and laryngeal or tracheal injury and their long-term sequelae, or infectious complications, such as sinusitis or nosocomial pneumonia. The pathophysiology of nosocomial pneumonia relies on the presence of bacterial colonization of the pharyngeal and/or upper gastrointestinal tract leading to repeated microinhalations of contaminated secretions from around the endotracheal tube. Indeed, endotracheal intubation bypasses the anatomical defense barriers of the upper airways. Nosocomial pneumonia is responsible for longer hospital stays as well as an excess in mortality, as recently demonstrated (8). Indirectly, the need for heavy sedation and some of the difficulties in weaning may also be attributed to the presence of false airways. To avoid these complications during acute exacerbation of COPD, noninvasive ventilation may be delivered at an early stage as a preventive means to avoid further deterioration or to deliver adequate ventilatory support at the time that endotracheal intubation seems mandatory. This latter procedure, often uncomfortable for the medical team to perform, requires adapted and optimized equipment but allows one to readily appreciate the efficacy of the technique.

### B. Providing Ventilatory Support in Patients for Whom Intubation Is Questionable

For some patients, endotracheal intubation and mechanical ventilation may not be desirable (9,10). Withholding this technique may be justified when a poor short-term prognosis is expected due to age and/or the severity of underlying disease combined with a high likelihood of serious complications. For instance, mechanical ventilation is sometimes not used in elderly patients (9). A decision not to intubate a patient is usually based on a combination of the wishes of the physician in charge, the patient, and his or her family. Also, high probability of a subsequent need for long-term mechanical ventilation combined with the impossibility of

such therapy for any reason may make intubation highly questionable. Patients with acute exacerbation of chronic lung disease while intubated and mechanically ventilated may occupy beds for many weeks with a relatively poor short-term prognosis, and in some countries the choice of therapy is often conservative, using medical treatment alone (10). To deny such treatment may condemn the patient to a premature death during the acute illness. For such patients, noninvasive ventilation may offer adequate treatment of respiratory distress with a much lower risk of complications (9–11.)

Because the above-mentioned decision may be very difficult, noninvasive ventilation may be used to postpone endotracheal intubation. The extra time can be used to improve one's knowledge of the previous history of the patient.

## III. Modalities of Noninvasive Ventilation

### A. Perithoracic Ventilation

#### *Technique*

Because the physiological action of the inspiratory muscles is to decrease intrathoracic pressure, it has seemed logical, in cases of failure of this musculature, to try to reproduce this action by means of a perithoracic negative pressure. Many devices have been proposed, mainly for neuromuscular disorders, including the iron lung, cuirass, or poncho wrap ventilators (12,13). Most of these ventilators and devices used conventional respiratory frequency. Recent devices synchronize spontaneous activity and negative pressure swings.

In a tank ventilator, the whole body, except the head and the neck, is submitted to intermittent negative pressure, whereas with the two other techniques only the thorax and the abdomen (poncho) or the thorax alone (cuirass) are submitted to the changes in pressure. Cuirasses have also been used to deliver negative pressure high-frequency oscillations (14). Finally, inflatable vests have been used in COPD patients to deliver positive pressure high-frequency oscillations (15).

#### *Physiological Effects*

In patients with COPD, several studies have demonstrated the ability of negative pressure perithoracic ventilation to reduce the electrical and mechanical activity of inspiratory muscles, allowing them to rest. In stable patients with chronic respiratory insufficiency or in inspiratory loaded spontaneously breathing normal subjects, Rochester and coworkers showed a considerable reduction in electromyographic diaphragmatic activity using a tank ventilator (Fig. 1) (16). Negative pressure ventilation was shown to be effective for treatment of acute exacerbations of chronic lung disease in the 1950s, and more recent reports have tried to

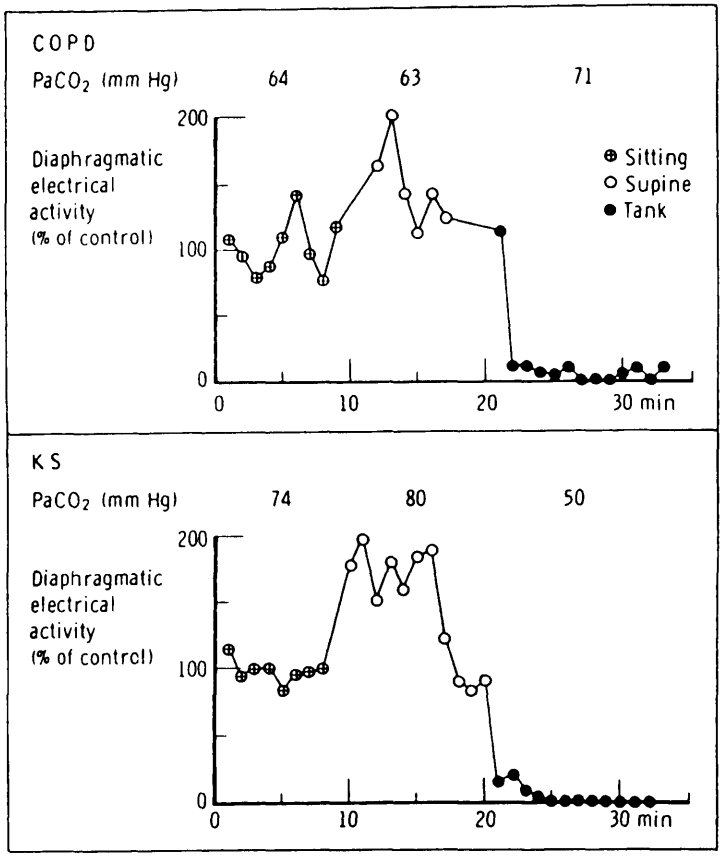


**Figure 1** Effect of negative pressure tank ventilator on diaphragmatic electrical activity in two stable chronically hypercapnic patients, one with COPD (top panel), one with kyphoscoliosis (lower panel). The marked decrease in diaphragmatic activity was coincident with an improvement in breathlessness. (From Ref. 16.)

confirm these observations (17–24). Several studies suggested beneficial effects of 6- to 8-hour periods of negative pressure ventilation on gas exchange in patients with mild or moderate decompensation of COPD (18–20). For instance, Sauret and coworkers used a poncho wrap ventilator associated with an oxygen mask to treat 17 COPD patients with severe COPD ($FEV_1$ lower than 1 liter) and mild decompensation (19). They were able to improve oxygenation by increasing face mask oxygen concentration without further reduction in alveolar ventilation or even with a slight improvement in $Paco_2$ and pH. In fact, most of the literature

concerning negative pressure ventilation in the field of acute respiratory failure does not indicate that these types of treatment are effective in reaching the goals of noninvasive ventilation as defined above. Most studies only describe short-term effects, have no or questionable control groups, and suggest only a mild efficacy.

Side effects reported, mainly during chronic use of these techniques, include obstructive sleep apneas and back pain (3). The use of negative pressure ventilators is also limited by the scarcity of the equipment and because the apparatus may restrict routine ICU procedures.

Interesting effects have been described with external high-frequency oscillations in stable COPD patients. In a study by Piquet et al., oscillations delivered during expiration only were able to induce dramatic changes in the breathing pattern of the patients with a subsequent decrease in the pressure-time index of the diaphragm (15). Again, however, the experience with such techniques during acute respiratory failure is extremely reduced.

### B. Facial Positive Pressure Ventilation

#### *Ventilatory Modes*

##### Continuous Positive Airway Pressure

Classically continuous positive airway pressure (CPAP) and more commonly positive end-expiratory pressure (PEEP) have been considered to be contraindicated for patients with COPD (25) chiefly because the addition of PEEP had the potential for worsening hyperinflation, a major factor inducing abnormal respiratory mechanics in COPD patients. The description of dynamic hyperinflation in such patients responsible for a positive value of respiratory system elastic recoil pressure at end expiration, however, has caused this view to change (26,27). Indeed, the addition of external positive pressure has been shown to counteract some of the deleterious effects of dynamic hyperinflation in intubated patients (28–30). When flow limitation is the cause of dynamic hyperinflation, external PEEP may reduce the positive mouth-to-alveolar pressure gradient that exists at the beginning of inspiratory muscle activity, reducing the inspiratory work of breathing (26–28). In seven intubated COPD patients, Petrof and coworkers showed an approximately 30% reduction in the pressure time product of the diaphragm and of the respiratory muscles with 10 $cmH_2O$ of CPAP compared to spontaneous breathing, this reduction reaching 40% with 15 $cmH_2O$ of PEEP (29). The increase in lung volume was around 240 ml, but it reached twice this value at 15 $cmH_2O$. In addition, all patients reported a reduction in dyspnea during the administration of CPAP. In nonintubated patients very few data are available on the effects of CPAP. Miro and colleagues used mask CPAP at 5 or 10 $cmH_2O$ in seven hypercapnic alert COPD patients (31). CPAP improved gas exchange in five, but one was withdrawn because of side effects and was intubated. Another was intubated while gas exchange deteriorated. The small number of patients and

the absence of control group make these results very preliminary. More interesting seems the combination of CPAP and pressure support ventilation, which has been proposed by several authors (32–34). Appendini and coworkers demonstrated that the combination of these two types of ventilatory support had a greater efficacy than each one alone to reduce inspiratory muscle work (32). The place of CPAP, even combined with inspiratory assist, is still unclear for two reasons. First, the reduction in inspiratory muscle activity may be accompanied by an increase in expiratory muscle activity, and in some instances the reduction in total work may become questionable (35). Second, the use of CPAP may increase the incidence of side effects such as leakage around the mask or gastric insufflation, which may limit its use in clinical practice. In a study by Fernandez and coworkers, low levels of external PEEP were successful in only 4 among 14 patients experiencing episodes of acute exacerbation of COPD, while it generated excessive leaks in the others (33).

### Intermittent Positive Pressure Ventilation

Volume-targeted or pressure-targeted modes can be used. Assist-control ventilation can be used with the usual settings for volume, breathing frequency, and inspiratory flow rate. Since it is volume targeted, leakage will decrease the volume delivered to the patient.

Pressure support ventilation has been used by many researchers (5,6,11,33, 36–38). This mode of ventilation has been shown in intubated patients to efficiently decrease the work of breathing, increase tidal volume, and reduce the spontaneous breathing frequency (39–41). It is usually easy for the patient to adapt to and is often comfortable for dyspneic patients (41). During noninvasive ventilation, leaks are counteracted by maintaining constant inspiratory pressure. Leaks may cause problems in the cycling mechanism from inspiration to expiration, and some researchers therefore used assist pressure-control ventilation in which the inspiratory time is preset.

### Rate of Delivery of Ventilatory Support

In most clinical series, noninvasive ventilatory support was delivered intermittently (4–6,9,33,36,51,58). For many researchers the duration of ventilation was maximal on the first day, up to 12–16 hours per day or almost continuously with periods of 10–20 minutes where the assistance was stopped, allowing the patient to drink, expectorate, or simply rest (6,37,58). On subsequent days the duration of ventilatory assistance was gradually reduced depending on the clinical status of the patient. Intermittent periods of 2–4 hours were sometimes used with periods of rest in between. The total duration of ventilatory assistance was remarkably short in most series, ranging from a total of $8 \pm 4$ hours in the study by Fernandez (33) to $3 \pm 1$ day in the study by Brochard (6) or $4 \pm 2$ days in the study by Wysocki

(36). Weaning from mechanical ventilation seems to be much simplified, with no interference from sedative drugs or false airways.

### *Physiological Effects*

Meduri and coworkers were among the first to describe their experience with noninvasive ventilation (5). In their initial report, they showed that they were able to improve respiratory status in six patients admitted for hypercapnic respiratory failure and in four patients with mainly hypoxemic respiratory failure. Blood gas abnormalities were partially corrected, and the three failures—patients who eventually required endotracheal intubation—were not related to failure of ventilation itself. Most patients were treated with full face mask ventilation using pressure support or pressure control ventilation. In a subsequent open study, the same authors described treatment of hypercapnic respiratory distress in 18 patients using pressure support ventilation combined with CPAP and, for some, the addition of mandatory mechanical breaths, using intermittent mandatory ventilation with pressure support and PEEP (11). In 13 of these 18 patients intubation was avoided, and the authors noted that an initial 2-hour improvement in $P_{CO_2}$ and pH was a good predictor of the success of the technique (absence of intubation). In addition, in a subgroup of seven patients, face mask ventilation was applied because of postextubation hypercapnic respiratory distress. Then within a few hours the authors compared ventilatory parameters and gas exchange measured during assisted ventilation delivered via an endotracheal tube or via a full face mask. No difference was noted between the two periods, indicating that assisted ventilation may be delivered noninvasively with the same immediate efficacy as through an endotracheal tube in these circumstances (Fig. 2).

Physiological studies concerning the effects of noninvasive pressure support ventilation on breathing pattern and respiratory muscle activity have been reported in patients with COPD (6,42). Comparable results have been obtained in several but stable COPD and in patients admitted for acute exacerbation of their disease. Delivered noninvasively, pressure support assists each spontaneous breath and is able to reduce transdiaphragmatic pressure, the pressure-time index of the respiratory muscles, or diaphragm electromyographic activity (Fig. 3). This reduction in muscle effort is accompanied by alterations in breathing pattern with increase in tidal volume, reduction in breathing frequency, and a significant increase in minute ventilation. Arterial blood gases are improved with an increase in oxygenation parameters and a concomitant increase in alveolar ventilation. In a physiological study in 11 patients admitted for acute exacerbation of COPD, Brochard and coworkers showed that 45 minutes of inspiratory positive airway pressure induced a rise in pH from $7.31 \pm 0.08$ to $7.38 \pm 0.07$, a drop in $P_{CO_2}$ from $68 \pm 17$ to $55 \pm 15$ mmHg, while $Pa_{O_2}$ was increased from $52 \pm 12$ to $69 \pm 16$

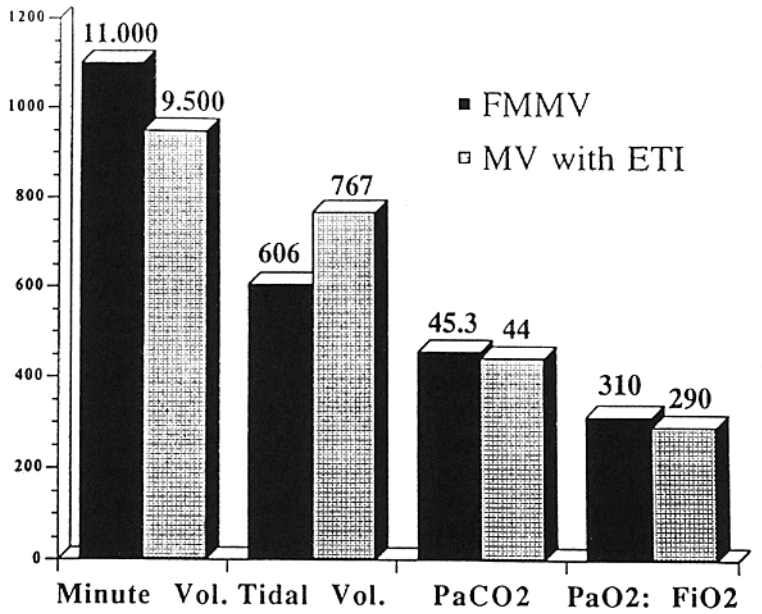


**Figure 2** Comparison of minute ventilation (Minute Vol.), tidal volume, $Paco_2$ and $Pao_2$:$Fio_2$ ratio in seven patients mechanically ventilated successively via an endotracheal tube (MV with ETI) or via a full face mask (FMMV), because of respiratory distress occurring early after tracheal extubation. No difference was noted between the two periods. (From Ref. 11.)

mmHg (6). The level of pressure applied seemed to influence the magnitude of the decrease in $Paco_2$ as shown in Figure 4. In addition, the magnitude of the drop in $Paco_2$ under pressure support was highly correlated with the reduction in breathing frequency, a physiological parameter easy to monitor at the bedside (Fig. 5). Therefore, this method is able to increase oxygenation without any concomitant rise in $Paco_2$ as usually observed with oxygen alone in COPD patients. For instance, Fernandez et al. showed that a rise in $Paco_2$ from 68 ± 18 to 92 ± 13 mmHg was observed when $Po_2$ was increased from 42 ± 12 to 98 ± 90 mmHg with supplemental oxygen in 13 COPD patients who had developed respiratory distress (33). In the same patients, administration of pressure support ventilation via a full face mask reduced $Paco_2$ to 67 ± 13 mmHg while a similar level of oxygenation was maintained. In six stable hypercapnic patients with COPD, Nava and coworkers showed that beneficial changes in gas exchange were associated in all with a substantial reduction in diaphragmatic EMG (42). In a study by Carrey and colleagues, a reduction in diaphragm EMG was demonstrated

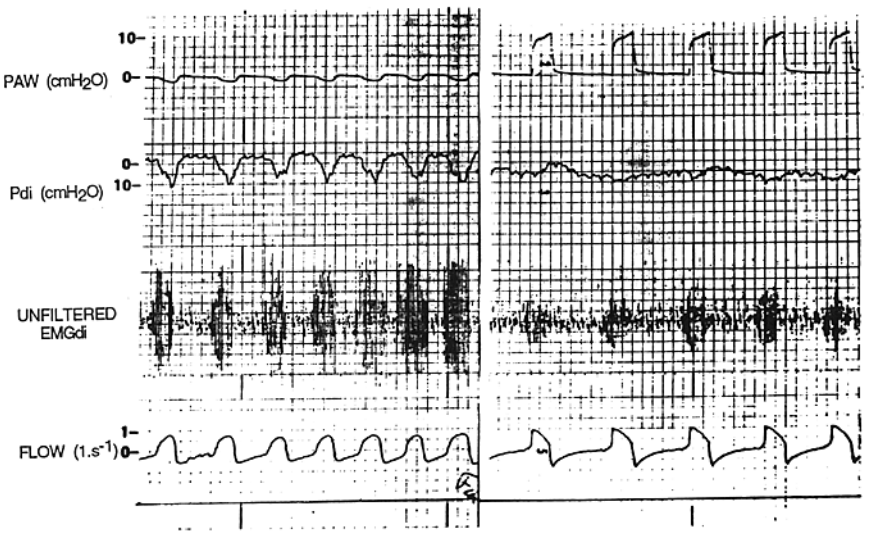


**Figure 3** Tracings of airway pressure (Paw), transdiaphragmatic pressure (Pdi), electrical activity of the diaphragm (Edi) and flow (V) measured in a COPD patient admitted for acute exacerbation, during baseline (left panel) and during noninvasive ventilation with inspiratory positive airway pressure (similar to pressure support) (right panel). Note the dramatic reduction in respiratory muscle activity concomitant with modifications in breathing pattern. (From Ref. 6.)

with nasal positive pressure ventilation in normal subjects as well as in patients with obstructive or restrictive chronic lung disease, although electromyographic changes were small for the low levels of pressure in COPD patients (43). In the study by Brochard, a reduction in diaphragmatic pressure time index and diaphragmatic EMG was demonstrated in nine patients with acute respiratory distress (6). The level of muscular effort remained substantial in some patients, however, suggesting that modest efficacy may be expected in some patients (Fig. 6).

## IV. Influence of the Equipment

### A. Mode of Ventilation

It is interesting to note that the effects of intermittent positive pressure breathing (IPPB) are markedly different from those of pressure support when delivered in nonintubated subjects, especially in a situation of high ventilatory demand. Mancebo and coworkers demonstrated that breathing with IPPB could cause extra work of breathing due to the superimposed impedance of the respiratory circuit

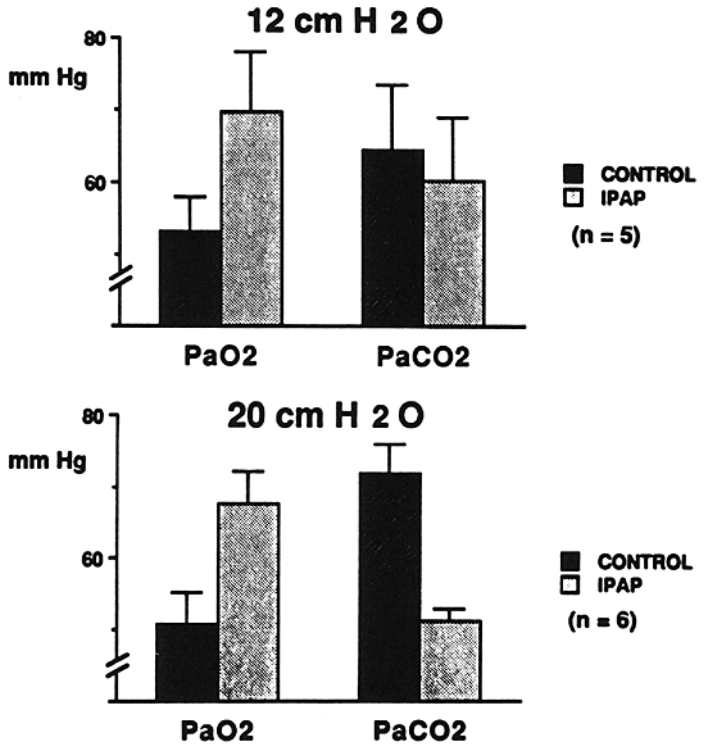


**Figure 4** Comparison of the respective efficacy of 12 $cmH_2O$ and 20 $cmH_2O$ of noninvasive pressure support on arterial blood gases in two groups of COPD patients admitted for acute exacerbation. The reduction in $Paco_2$ was much more pronounced with 20 $cmH_2O$. (From Ref. 6.)

and of the poor response of the ventilatory device (44). This emphasizes the importance of the ventilatory mode in situations of ventilatory failure and/or high ventilatory demand.

Pressure support ventilation and assist-control ventilation have been the two most frequently used ventilatory modes, with or without PEEP. During assist-control, the patient triggers the breath and usually receives a preset tidal volume at constant flow. The influence of the peak flow setting on the work of breathing has been repeatedly demonstrated in intubated patients (45,46). High peak flow rates are essential to significantly reduce the patient's effort and work of breathing. The flow rate is often set in the range of 45–100 liters/min, resulting in high proximal peak airway pressure at the end of inspiration. This may be enhanced during noninvasive ventilation because of the possibility of air leaks through the mask. In

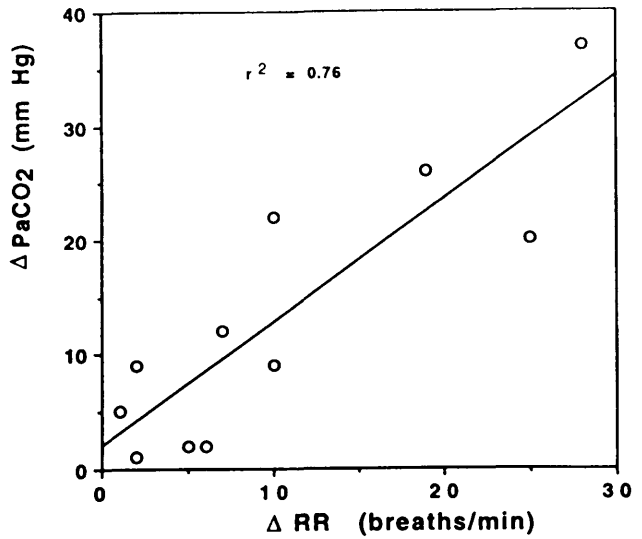


**Figure 5** Presence of a significant correlation between the drop in $Paco_2$ ($\Delta Paco_2$), and the observed reduction in respiratory rate ($\Delta RR$) after 45 minutes of noninvasive ventilation with pressure support delivered via a face mask in 11 COPD patients. (From Ref. 6.)

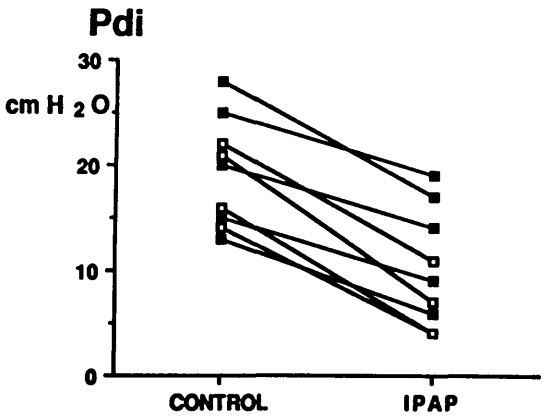


**Figure 6** Reduction in the mean transdiaphragmatic pressure generated at each breath, from baseline (control) to noninvasive pressure support (IPAP) in nine COPD patients with hypercapnic respiratory failure. Note that diaphragmatic activity is significantly reduced but not abolished. (From Ref. 6.)

addition, as discussed earlier, in a volume-targeted mode, leaks result in a reduction of the amount of assistance delivered to the patient. Although some comparative data are available in intubated patients, very few have been obtained during noninvasive ventilation. Vitacca and coworkers compared the clinical efficacy of the two modes of ventilation in a randomized study in 29 COPD patients (37). Although the efficacy of the technique was similar in the two groups in terms of absence of need for endotracheal intubation (88% for PSV and 77% for IPPV), the compliance with treatment was better and the side effects were fewer with pressure support. This may be explained by the higher peak mask pressure generated with IPPV and the lower level of comfort often found with assist-control.

Although the effects of pressure support ventilation have been well described in intubated patients, the efficacy of the technique may differ markedly from one ventilator to another. Indeed the algorithm to deliver the pressure is often manufacturer-specific, and it has been shown that these characteristics may influence the patient's work of breathing and breathing pattern (47,48). Many devices were initially designed for stable chronic patients to use during home mechanical ventilation, and the same degree of efficacy may not be observed with these devices during acute ventilatory failure. The differences among devices could relate to trigger sensitivity, the rate of rise in pressure and the initial peak flow rate, the plateau wave shape, and the cycling mechanism from inspiration to expiration. In addition, the flow-impending characteristics of the expiratory circuit and the possibility of generating rebreathing for ventilators without separate inspiratory and expiratory lines may play a role in the clinical efficacy of this mode of assistance (49).

### B. Patient-Ventilator Interface

In patients with chronic respiratory failure, noninvasive ventilation is usually delivered through nasal masks (2,3,50,51). Commercially available models can be used, and high-quality masks in many sizes are now available. Customized masks can be individually molded to the patient's nose in silicone paste mixed with a slow catalyzer. This preparation usually requires about 30 minutes. Masks are secured to the head with straps.

In the acute care setting, many clinicians are using full face masks (5,6,33, 36,37). Nasal masks, however, present many advantages compared to full face masks, including better comfort for the patient, easier use, and lower deadspace. However, during nasal ventilation, inadvertent loss of volume through the mouth may be a major problem. Carrey and coworkers have shown that during nasal positive pressure ventilation, the position of the mouth is crucial to the efficacy of the technique to reduce respiratory muscle activity (Fig. 7) (43). Because gas insufflated through the nose may largely leak via the mouth, closure of the mouth is mandatory. This problem may be encountered during sleep in the setting of

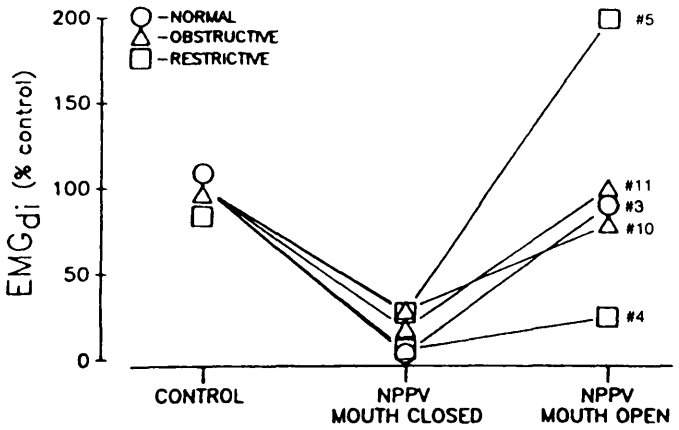


**Figure 7** The effect of mouth position on mean phasic diaphragm EMG during nasal positive pressure ventilation in normal subjects and in patients with restrictive or obstructive lung disease. The application of nasal ventilation with the mouth open resulted in reemergence of substantial diaphragmatic activity. (From Ref. 43.)

home mechanical ventilation, but it is particularly a problem in the ICU. Many patients with acute respiratory failure do not choose to breathe solely via the nose and are often not cooperative enough to do so on request.

Disadvantages of the full face mask are the high degree of discomfort or anxiety generated in some patients, the internal deadspace of the mask, and the difficulty in perfectly fitting the patient's face. Recently, efforts have been made by manufacturers to improve the quality of these masks.

### C. Influence of Equipment on Success of the Technique

As discussed below, very interesting results have been obtained using nasal masks and intermittent positive pressure ventilation in the assist-control mode as well as using pressure support ventilation delivered through a full face mask. Lack of efficacy of noninvasive ventilation and high incidence of failure in the treatment of acute respiratory distress in COPD patients have also been reported, however (52,53). Chevrolet and coworkers emphasized that the technique was a difficult and time-consuming procedure for nurses (53). It is also our experience that this technique is not always easy to apply in patients with acute exacerbation of COPD and that its acceptance both by patients and by medical as well as nonmedical staff may be a major limitation of the technique. It is likely that some training is necessary for the team before an optimal routine daily use of this technique can be expected. That is why technical aspects may be so important. It is of particular

interest to note that the group from Breschia initially reported a negative initial experience with the technique using nasal positive pressure ventilation (52). They compared the result of nasal ventilation with those of standard therapy in COPD patients assigned to one or the other treatment on the basis of their ability to tolerate nasal ventilation. Approximately half of the patients were not able to cope with the ventilatory mode, had a bad compliance, or refused noninvasive ventilation. No improvement could be demonstrated in the group treated with noninvasive ventilation. In a subsequent report, they found by comparison with an historical control group that the rate of intubation dropped from 46% (no assistance) to 23% (assist-control) or 12.5% (pressure support) with noninvasive ventilation (37). Although comparison with historical control groups must be interpreted cautiously in part because treatment standards may change over time, it is noteworthy that these authors changed from the use of a nasal mask to a full face mask. They also demonstrated better patient compliance with pressure support. In Chevrolet's experience, nasal ventilation and assist-control were also used, which may play a role in the difficulties encountered.

As already mentioned, leaks can be a major problem, causing discomfort and lack of efficacy. A volume-targeted mode has been proposed to increase the preset tidal volume. When a pressure-targeted mode is used and leaks are still present despite proper adjustment of the mask, Meduri has proposed adding several mechanical volume-targeted breaths using intermittent mandatory ventilation with pressure support (11). During pressure support ventilation leaks may cause an additional problem in the cycling from inspiration to expiration. This may be solved by using an adjustable flow threshold for cycling, by setting a limit for inspiratory time, or by using a time-cycled pressure-targeted mode (6).

## V. Clinical Results

Many interesting clinical results have been obtained in open uncontrolled studies. Most "favorable" results rely on the fact that the condition of the patients was severe enough to deem endotracheal intubation necessary either immediately or after a few hours of clinical deterioration (5,9,11,33,36,37,54,55). Meduri reported a 72% success rate in a group of hypercapnic patients, most of them experiencing COPD (11). Researchers who already had experience in the field of noninvasive home mechanical ventilation found good results when the same patients were admitted for acute exacerbation and treated with nasal ventilation in the ICU (4,56). Wysocki et al. assessed the effects of this technique in 17 consecutive patients with various causes of respiratory distress, both of the hypercapnic of the hypoxemic type (36). The overall success rate was 47%. However, successes were clearly more frequent in the hypercapnic group. Other studies reported success rates of 72% (9), 83% (54), or 78% (33), mostly in COPD

patients. Several problems, however, make interpretation of the data obtained in open studies difficult. First, selection criteria, or criteria for intubation, are often difficult to define and remain highly subjective, such as inability to protect upper airway or worsening of hypercapnia and acidosis under oxygen therapy. Second, although most results strongly suggest that noninvasive ventilation may reduce the need for intubation in carefully selected individual experiences, we do not really know to what extent this technique is applicable to other ICU settings. Third, the real rate of intubation is relatively difficult to predict based on arterial blood gas data alone, since the clinical tolerance of blood gas abnormalities vary greatly from one patient to another (57).

Recently, Bott and coworkers in a prospective randomized controlled study compared two groups of patients admitted for acute exacerbation of COPD in whom the same medical treatment was applied associated to nasal noninvasive positive pressure ventilation in one of the two groups (58). Physiological parameters were compared after one hour of allocated treatment on day 3 and day 7. Patients in the two groups had similar ages, arterial blood gases, and spirometry. There was a significant improvement in pH from 7.35 to 7.38 in the group treated with noninvasive ventilation, whereas pH fell from 7.33 to 7.31 in the control group after one hour. Visual analog scores over the first 3 days of admission showed less breathlessness in the group treated with noninvasive ventilation (Fig. 8). Finally, survival rates were compared in the two groups. In an intention-to-treat analysis, the difference was not significant. However, when the four patients who did not tolerate noninvasive ventilation were excluded from the analysis, the mortality rate became significantly lower in the treated group (4% vs. 30%; $p < 0.05$).

In a first study, we reported our initial experience in a series of 13 patients admitted for acute exacerbation of COPD (6). Results obtained in this group were analyzed in a case-control study, with each treated patient being matched with an historical control patient. A major significant reduction in the need for endotracheal intubation was observed between the two groups (8% vs. 85%), associated with a reduction in the length of ventilatory assistance (3 days vs. 12 days) and in the length of stay in the ICU (7 days vs. 19 days), all results being highly significant. On admission pH was 7.29, $P_{CO_2}$ 65 mmHg, and the $P_{O_2}/F_{IO_2}$ ratio 203 mmHg. These results seemed extremely promising but had several limitations. They were obtained in a single center, and their management may not reflect the daily routine care provided for these patients. Recently this experience has been extended into a multicentric randomized trial conducted in five European centers (59). Patients were included in the study when admitted for acute exacerbation of COPD with objective criteria for severity based on breathing frequency, pH, and $P_{CO_2}$. Patients with a clear and treatable cause of decompensation, such as pneumonia, need for surgery, pneumothorax, or acute myocardial infarction, were excluded from the study. Patients were randomized into a conventional group,

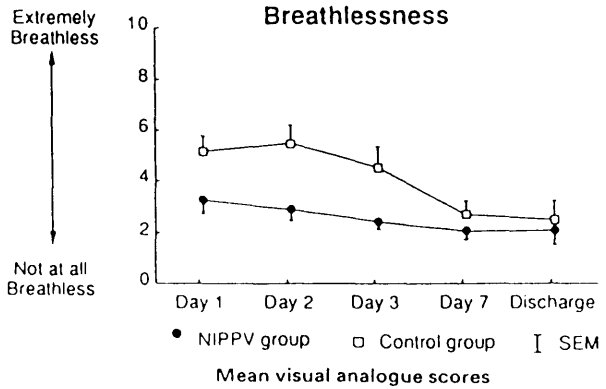


**Figure 8** Evolution of breathlessness estimated by the means of visual analog scores over several days in two groups of COPD patients treated for acute respiratory distress. Open squares indicate the control group, while closed circles indicate patients treated with noninvasive ventilatory support (NIPPV). The score was significantly lower in the NIPPV group. (From Ref. 58.)

where treatment included oxygen, antibiotics, and bronchodilatators, and a group where the same treatment was associated with systematic use of noninvasive pressure support ventilation delivered via a full face mask. Pressure support was delivered with a specially manufactured device designed to have a high sensitive flow-triggering system, a fast rate of pressurization, and low expiratory resistances. On admission, mean pH in the two groups was about 7.27, $P_{CO_2}$ around 70 mmHg, and $P_{O_2}$ 40 mmHg breathing room air. While the two groups were similar at admission, a significant difference in the need for endotracheal intubation was noted: 25% in the group treated with noninvasive ventilation versus 75% in the conventional group. In addition, statistical analysis indicated a significant reduction in the length of hospital stay and a marked reduction in hospital mortality (9% vs. 29%). Although these results were obtained in a carefully selected group, they indicate that major benefits can be expected from noninvasive ventilation in the treatment of COPD patients admitted for acute respiratory failure.

## VI. Complications of Noninvasive Ventilation

Complications reported with this technique are usually of minor severity. Their major consequence is, however, inability to use the technique. They include skin pressure lesions and facial pains, discomfort and inability to sleep, mask leakage, and gastric distension. Intolerance of the mask or maladaptation to the patient's face may be a major limitation to the use of noninvasive ventilation. In a study by

Meduri, 2 patients among 13 could not be properly ventilated without major leaks, and therapy was therefore withdrawn (11). One patient developed intolerance to the mask after 2 hours of treatment. Two patients developed mild facial pressure necrosis at the site of mask contact, which healed spontaneously in 2 days. Fernandez noted no significant side effects except nose pain among 14 episodes of treatment for acute respiratory failure (33). In the randomized study by the British group, of 30 patients randomized to the noninvasive ventilation group, 4 could not be ventilated: 2 because they could not cooperate, 1 because he was unable to breathe through his nose, and 1 because he requested the withdrawal of all active treatment (58). Comatose patients with a need to protect upper airways and patients with a frequent need to remove secretions may be difficult to treat with this technique, although these do not constitute absolute contraindications in all cases.

Gastric distension seems to be uncommon with pressure support ventilation when mask pressure is limited to 20 $cmH_2O$ (6). Therefore gastric suctioning is not recommended.

An increase in peak mask pressure augments the risk of leakage and of gastric distension. It also necessitates tightening the mask more closely, with an increased risk of side effects.

## VII. Conclusion

Noninvasive ventilation may impart considerable benefits to the treatment of acute respiratory failure of patients with COPD (3,6,58–61). Reduction in the need for endotracheal intubation seems now clearly demonstrated. Several reports strongly suggest that this may be associated with a reduction in the length of hospital stay and even in mortality. Confirmation of these results will make this therapy a gold standard in the treatment of COPD in the ICU.

A number of failures of the technique have been reported, and further efforts are needed to delineate the causes of failures. Part of the explanation may lie in the equipment used, and improvement in the type of assistance delivered to the patients is clearly needed. New forms of pressure-supported ventilation may bring new benefits. Contraindications of the technique are also not well defined. In particular, it is possible that some patients already stressed to the point of exhaustion may not benefit from partial ventilatory assistance but may require full support, which is usually better administered via endotracheal intubation.

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# 27

# Basic Physical Principles for Ventilators and Ventilatory Modes

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## I. Historical Approach and Recent Developments

The aim of mechanical ventilation is to maintain or restore normal gas exchange in patients with acute or chronic respiratory deficiency. For a long time, ventilators have been assigned to reproduce some of the modalities of normal spontaneous breathing, i.e., a forced tidal volume in the range 400–800 $cm^3$ (10–12 ml/kg) at an imposed frequency in the range 12–24 cpm (1). This mode was called controlled mechanical ventilation (CMV). It required machines capable of delivering a fixed tidal volume, or a constant flow, whatever the mechanical characteristics of the respiratory system (2). Accordingly, ventilators were often thought of only with respect to their ability to mimic spontaneous breathing pattern, with little consideration of the deleterious clinical consequences, especially in lungs with highly altered mechanical properties (3).

The major concern with CMV is not technical difficulties in generating the chosen ventilatory pattern (even though this task can be difficult for physical reasons explained below) but lies in the necessary adaptation of the patient to the machine. The latter necessitates deep sedation and sometimes paralysis of the respiratory muscles. Moreover, applying the CMV mode in highly altered lungs requires the generation of elevated alveolar pressure, applied to both the diseased

and the nondiseased lung regions. The most serious consequences are hemodynamic alteration, the risk of volo/barotrauma, and the risk of overinflation pulmonary edema, all of which tend to increase the risk of weaning failure contributing to longer stays in the intensive care unit (ICU) (3).

Reduction of these risks has become a key treatment goal. A variety of solutions have been proposed constituting new modes of mechanical ventilation: high-frequency ventilation (4,5), pressure support ventilation (6,7), permissive hypercapnia (8,9), and noninvasive ventilation (10,11). To what extent these new modes will be able to replace the standard CMV mode while minimizing the risks of barotrauma depends on ventilator-patient interaction and thus requires a deeper understanding of the physical principles involved in mechanical ventilators and monitoring systems. Thus, instead of presenting an exhaustive description of the ventilatory modes and ventilators available, which has already been done (12,13), we present in this chapter some fundamental aspects of the mechanical interaction between ventilator and patient.

In terms of new concepts of mechanical ventilation, an important innovation during the 1980s was so-called high-frequency oscillatory ventilation (HFOV) (4,5). With this mode, normal gas exchange was shown to be effective, with tidal volumes about 20% smaller than the anatomical deadspace and with lower alveolar pressure variations (14,15). Interestingly, the risk of barotraumatism was expected to be reduced with HFOV, thanks to a better gas exchange efficiency, which was supported by physical concepts basically different from the classical concept of alveolar ventilation. Unfortunately, after a decade of intense experimental and theoretical studies performed to understand its physiological mechanisms, the HFOV mode is now rarely used in adult ICUS. One reason for this is that efficiency of gas exchange, estimated in humans ventilated by HFOV, was not clearly improved compared to CMV (16), whereas lung volume and alveolar pressure oscillations were difficult to control (17). Another possible reason why HFOV was clinically unsuccessful is that full relaxation of patient respiratory muscles is basically required, as during the CMV mode.

A clear improvement was made with the design of the assist-controlled ventilation (ACV), which combined the advantage of controlled ventilation with the ability to maintain some patient ventilatory activity. It consisted of synchronizing volume-controlled time-cycled breaths with patient respiratory efforts. Its efficacy is not proven, mainly due to the persistence of a significant respiratory activity (18). Reduction of the patient respiratory workload also appears questionable with intermittent mandatory ventilation (IMV), a mode in which cycles of free spontaneous breathing are allowed in between mechanical cycles (19).

A decisive improvement has been made in providing pressure support assistance synchronized breath by breath with the inspiratory effort of the patient, both patient-initiated and patient-interrupted. With this mode, called pressure support ventilation (PSV), the contribution of inspiratory muscles depends on the

level of delivered positive pressure and on the rapidity of the machine in detecting respiratory effort. The higher the level of pressure support, the smaller the contribution of the patient and the work of breathing (6,7). Further improvement of the PSV mode was recently obtained when the inspiratory assistance was triggered by the inspiratory flow signal and the pressure plateau was obtained as early as possible in the inspiratory cycle (11). Proportional assist ventilation (PAV) is a new PSV mode in which the level of pressure support is proportional to the patient demand throughout the inspiratory cycle (20).

It might be surprising to consider that it took half a century to propose modes of mechanical ventilation compatible with residual respiratory muscle activity. This can be explained by the disappointing effect of old pressure modes, which often appeared "flow limited," i.e., forcing the patient to provide a non-negligible part of the inspiratory effort. There are reasons to believe that many of the problems of poor patient tolerance that delayed the diffusion of pressure modes were more related to the poor quality of circuits and pressure generators used than to the principle of the technique itself (21). Indeed, ventilators failed to maintain a sufficient pressure level as inspiratory flow was increased secondary to patient demand, whereas their dynamic response was too slow, i.e., the pressure reached the desired level at the end of inspiration, when the pressure assistance was no longer needed by the patient. Up until the 1970s, little attention was paid to the interaction between the ventilator and the patient. Twenty more years passed before mechanical ventilation was considered a variable and complementary part of the patient effort. It is now admitted that pressure assist modes are much easier to adjust to the patient's needs than the standard volume-controlled modes (CMV). Although the exact pattern of the optimal pressure assistance to be delivered is still under debate (11,20), it appears that the optimal mode will have to integrate more and more knowledge of mechanical and physiological variables and their evolution with time. Similarly, knowledge related to therapeutic strategies might be advantageously integrated. This may require using artificial intelligence techniques developed to perform intelligent monitoring and to assist the clinical staff in the difficult task of making medical decisions (22).

## II. Physical Principles Used in Fluidic Flow and Pressure Generators

To provide all or part of the gas transport necessary to assist or control ventilation, ventilators use different driving systems. It has not often been clearly stated that ventilator efficiency depends on the characteristics of the chosen driving system. Basically, driving systems include either mechanically driven moving pieces (pistons, arms, bellows) which are moved by an engine, or fluidic systems (e.g., nozzles, turbulent jets), which require a source of compressed gas. The efficiency

of mechanically driven systems strongly depends on the power of the engine. Such systems were used early in the development of mechanical ventilation and have been reviewed in classical textbooks (2,23). In contrast, fluidic systems, or more precisely pneumatic gas systems, have been more recently introduced into clinical practice. Unfortunately, they have often been confusingly described in textbooks on mechanical ventilation.

Ventilators are usually classified in two categories (23): (1) flow generators, which deliver inspiratory flows as independent as possible from the mechanical properties of the respiratory system, and (2) pressure generators, which presumably generate an airway pressure level as independent as possible from inspiratory flow. Modern ventilators generate a variety of modes, including these two modes and/or intermediate modes.

To compensate for the difference between the effect produced at the level of the driving system and the desired effect, modern ventilators include servo-controlled electrical or fluidic systems. Obviously the smaller the difference between the actual effect and the desired effect, the easier the regulation. This is why it is still desirable to optimize driving systems. In general, flow generators are easier to regulate than pressure generators because flow is preserved through the inspiratory line, while pressure is "lost" through friction resistance. This problem may be solved by placing the measuring devices (pressure and flow transducers) as close as possible to the airway opening.

This chapter presents a critical review of basic pneumatic systems now widely used in modern ventilators most likely because they seem to be easier to control than systems with mechanical moving pieces. We believe that some important aspects of fluid dynamics must be reviewed in order to understand the effects of mechanical ventilation.

### A. Flow Generators

The basic pneumatically driven flow generator is made of a source of compressed gas (3–5 bars) incorporating an adjustable resistance (2). The adjustable resistance usually consists of an orifice, the size of which may be adjusted as shown in Figure 1. If the resistance is sufficiently large, i.e., the size of the orifice is sufficiently small, this system should deliver a flow independent of patient conditions and thus behave as a constant flow generator. This belief is based on the reasoning that pressure drop through the resistor is up to 35 times the maximum pressure developed through the respiratory system, or maximum pressure developed at airway opening. However, classical results of fluid dynamics reviewed below demonstrate that an orifice flow is not totally independent of downstream pressure.

Application of the Bernoulli theorem to incompressible fluids during passage through orifices, such as a hole in a thin wall, a nozzle, or a Venturi (Fig. 2),

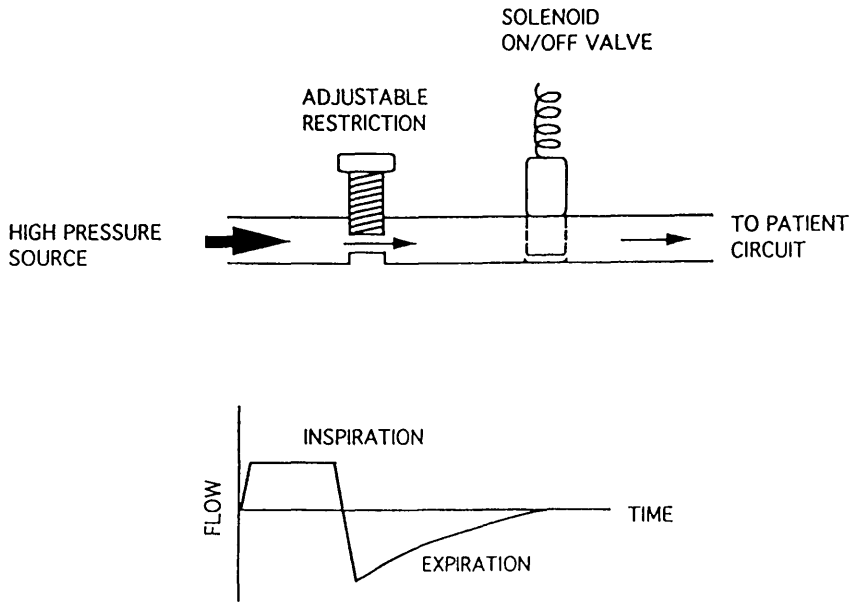



**Figure 1** Any adjustable restriction placed in a high-pressure circuit connected to the patient is assumed to provide an "ideal" constant flow generator. Steady flow theory of compressible fluids reveals that only orifices with a geometry able to minimize energy losses, such as nozzles, are able to generate a constant mass flow. Under these conditions, volumetric flow, inversely related to gas density, may be decreased by 10% if airway pressure, i.e., gas density, is increased from 0 to 100 $cmH_2O$ secondary to the mechanical alteration of the respiratory system.

leads to parabolic relationships between flow ($\dot{V}$) and pressure drop ($P_1 - P_2$), or between flow ($\dot{V}$) and pressure ratio ($P_2/P_1$):

$$\begin{aligned} \dot{V} &= \alpha\ S\ [2(P_1 - P_2)/\rho]^{0.5} \\ &= \alpha\ S\ (2P_1/\rho)^{0.5}\ [1 - (P_2/P_1)]^{0.5} \end{aligned} \quad (1)$$

where S is the minimal area of the passage and $\rho$ the gas density at the upstream pressure $P_1$. $P_1$ and $P_2$ are the pressures, respectively, upstream and downstream of the orifice. $\alpha$ is a correction coefficient varying from 0.5 to values higher than 1, depending on the inner shape of the passage, as shown in Figure 2. $\alpha = 0.6$ for an orifice in a thin wall, $\alpha = 0.8$ for a cylindrical passage, and $\alpha \approx 1$ for passages with hydraulic convergent shape (24,25). $\alpha$ actually represents the ratio between the constricted area of the fluid vein and the minimal area of the passage.

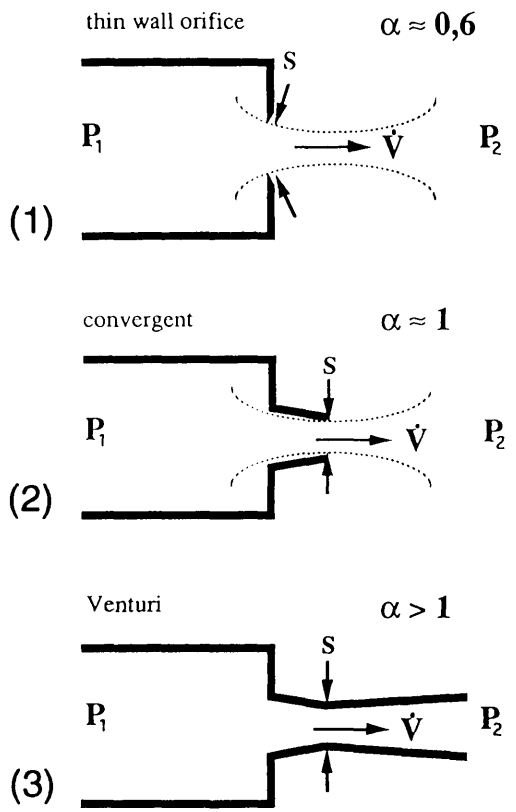



**Figure 2** Orifices with different geometrical shapes—thin wall, convergent, Venturi—at the exit of a reservoir pressurized at a given pressure, $P_1$, generate different flows, $\dot{V}$, the value of which depends on (1) a correction coefficient, $\alpha$, (2) upstream to downstream pressure difference $P_1 - P_2$, and (3) gas density, $\rho$. $\rho$ is presently taken to be constant and fixed by upstream conditions (incompressible fluid).

Equation (1) confirms that flow of an incompressible fluid across a resistive orifice necessarily depends on the shape of the orifice as well as on upstream and downstream pressures $P_1$ and $P_2$. Due to the parabolic shape of the relationship between flow and pressure ratio, the decay in flow across the orifice is slow when downstream pressure is well below upstream pressure [see Eq. (1), $P_2 \ll P_1$].

Due to the elastic, or compressible, behavior of gases, Eq. (1) does not apply to gases when pressure ($P_1$) upstream of the orifice markedly differs from downstream pressure ($P_2$). This is obviously the case if such a system is used to generate mechanical ventilation: gas source pressure available in Intensive Care Units is 2–

3 bars (2000–3000 $cmH_2O$), whereas the maximum airway pressure is much lower, below 100 $cmH_2O$. The orifice flow-pressure relationship, analogous to Eq. (1) but taking into account the compressible characteristics of gases, is presented in Figure 3. To describe flow phenomena of compressible fluid through orifices, the pertinent quantity is the mass flow rate $\dot{V}m$, defined as the product of density and volumetric flow ($\dot{V}m = \rho\dot{V}$). Theory of compressible fluids demonstrates that mass flow rate actually depends on the orifice geometry. An ideal orifice geometry would generate no friction and, below a critical value of the pressure ratio ($P_2/P_1 < 0.527$ in air), a mass flow independent of downstream pressure. Such an ideal orifice geometry is called a nozzle, i.e., an aerodynamic convergent

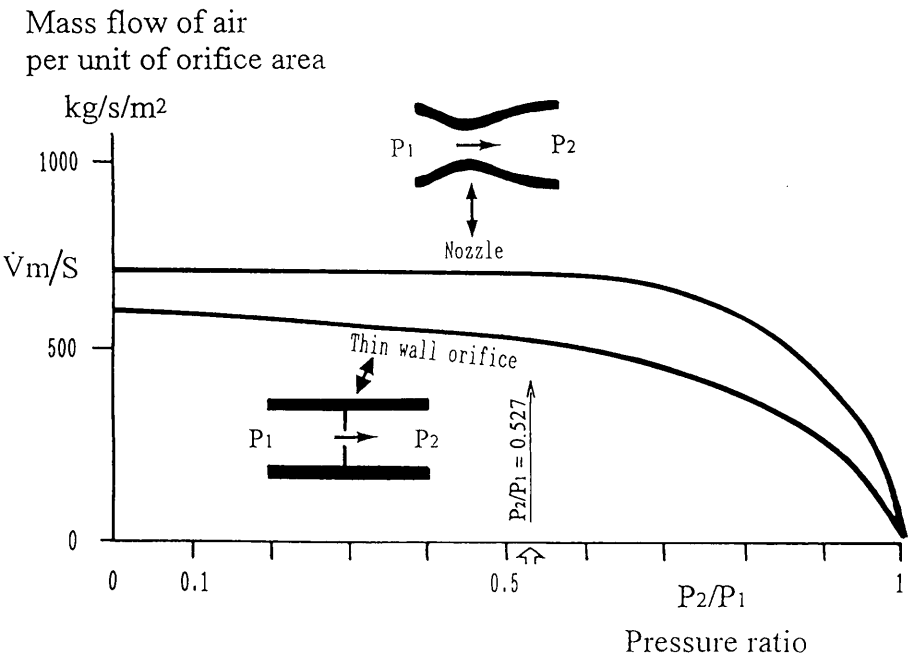



**Figure 3** Flow-pressure relationship of a compressible fluid, i.e., a gas ($\rho$ varies as fluid experiments the pressure decrease from $P_1$ to $P_2$), through two kinds of orifices: a nozzle and a thin wall orifice. The mass flow per unit of orifice area [$\dot{V}m/S = \dot{V}\rho/S$ in $kg/sec/m^2$ = $(m^3/sec)(kg/m^3)/m^2$] is plotted versus the downstream to upstream pressure ratio, $P_2/P_1$. Below a critical value of the pressure ratio—$P_2/P_1 = 0.527$—the mass flow rate of compressible fluids becomes independent from downstream pressure, $P_2$, but still depends on upstream pressure $P_1$ [see Eq. (2) in text]. Note that the plateau of mass flow is altered in orifices susceptible to generate nonnegligible energy losses such as thin wall orifices.

terminated or not by a gentle divergent (see Fig. 3). The maximum mass flow possible (in air) through a nozzle is given by the following equation (24):

$$\dot{V}m = 0.0404 \cdot S \cdot P_1/(T_1)^{0.5} \quad (2)$$

in which $\dot{V}m$ (in kg/sec) depends on the cross-sectional area of the throat, S (in $m^2$), and on the gas physical conditions upstream the orifice: absolute pressure $P_1$ (in Pascal) and absolute temperature $T_1$ (in K). Importantly, $\dot{V}m$ does not depend on the pressure difference across the nozzle as long as $P_2/P_1 < 0.527$ is verified (in air). This flow limitation effect, like the well-known "waterfall" effect, results from the coupling between (1) the mass conservation equation, which predicts that maximum velocity necessarily occurs in the minimal area of the nozzle, the so-called nozzle throat, and (2) the energy conservation associated with a reversible thermodynamic process, which predicts that gas velocity in the throat cannot exceed the local speed of sound.

In classical textbooks on respirators (2), the flow limitation property of nozzles has been mistakenly extended to any orifice shape, but only nozzles behave in this way. Figure 3 shows that Eq. (2), which applies to nozzles, tends to overestimate the flow through a thin plate hole of similar size. This is because due to the constriction of the fluid vein, the actual area of the fluid stream downstream of the thin plate hole is smaller than the orifice area, whereas due to the effect of frictional losses, the flow cannot remain constant. A wide variety of flow-pressure curves may be obtained, depending on the orifice geometry.

To what extent a constant "mass flow" ($\dot{V}m$) in a nozzle provides a constant "volumetric flow" ($\dot{V}$) in the patient obviously depends on gas density ($\rho$), i.e., on the absolute pressure at which the patient is ventilated. Assuming that Eq. (2) is true (sonic flow regime), a 100 $cmH_2O$ increase in lung insufflation pressure ($P_2$) corresponds to a 10% increase in gas density. The latter effect would result in a 10% decrease in volumetric flow ($\dot{V}$), keeping the source pressure ($P_1$) constant. Incidentally, in the subsonic flow regime, the same effect would produce a larger decrease in volumetric flow rate due to the higher dependence on downstream pressure $P_2$.

These results demonstrate that when nozzles are used as flow generators, gas flow is kept constant within 10% in most conditions practically encountered in CMV ($P_2 < 100$ cm $H_2O$). However, using orifice geometry differing from nozzle geometry, constant flow may still be obtained using a servo-controlled mechanism that adjusts pressure upstream of the orifice ($P_1$) in such a way that flow, usually measured in the ventilator, remains constant.

### B. Pressure Generators

Many pressure generator systems constructed in the past did not offer satisfactory steady and dynamic performances (2) (Fig. 4). For instance, airways were ade-

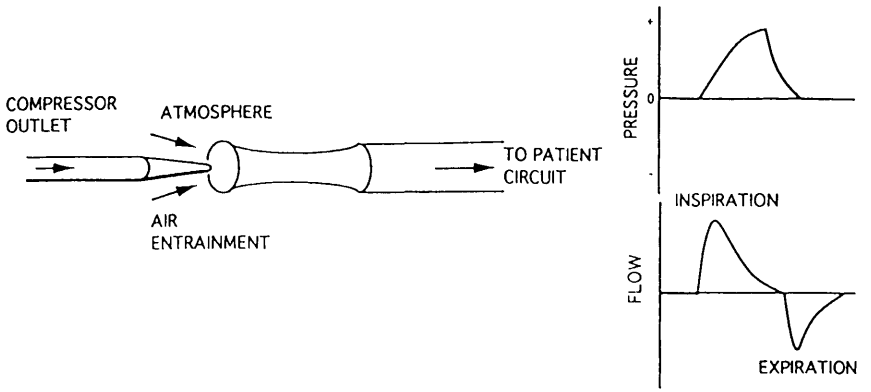



**Figure 4** A turbulent jet confined in a tube whose entry is opened to the atmosphere and the exit connected to the patient circuit constitutes a pressure generator. This "fluidic" driving system, inappropriately called a Venturi system in many textbooks, is usually presented as a "nonideal" pressure generator because it does not generate a flow-independent pressure. Such a system may, however, be considerably improved if an appropriate geometry of the jet mixing chamber is used and if inspiratory circuit resistance is minimized (see Fig. 8).

quately pressurized only when the flow needed by the patient was below a moderate value, i.e., when the assistance was no longer useful since patient inspiratory effort had been already developed. This problem is illustrated in Figure 5 for a commercially available pressure ventilator. This is probably the reason that pressure generators tended to be rapidly abandoned in favor of classical flow ventilators, considered to be more reliable. The reason for such a failure is that pressure generators were indeed "flow limited," i.e., unable to deliver the desired quantity of gas at the pressure chosen by the clinician.

To pressurize an unlimited quantity of gas at a pressure in the range of 10–30 $cmH_2O$, the most appropriate pneumatic system is a turbulent jet confined in a tube with one extremity opened to atmosphere. This system, described in Figure 6, was used in a nonoptimized fashion in early pressure generators (Fig. 5), but also to mix air and oxygen during oxygen therapy (26).

The confined turbulent jet is sometimes inappropriately called a Venturi system in the field of mechanical ventilation (2). However, due to the mixing of the jet with the surrounding air, the turbulent confined jet consumes most of the jet kinetic energy in friction secondary to high radial velocity gradients and swirling, while, by principle, energy losses remain negligible in the Venturi system (27).

As the jet dissipates in the tube, the constant physical quantity to consider is the total thrust, i.e., the sum of the momentum flux, $\rho \dot{V}^2/S$, and of the pressure

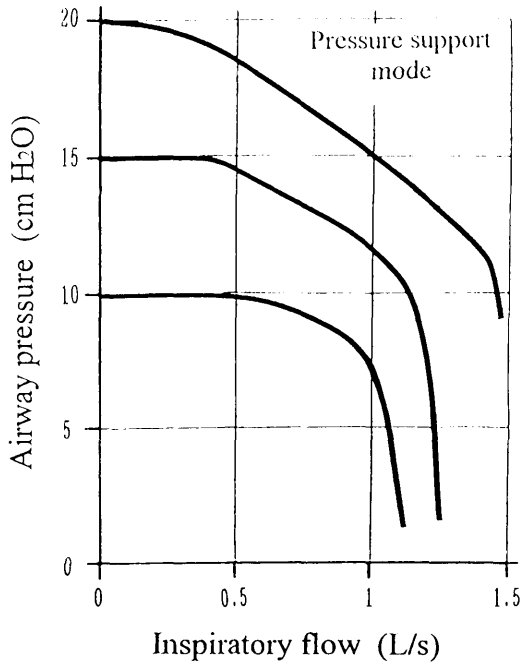



**Figure 5** A typical "airway pressure"–"inspiratory flow" relationship obtained in a "flow-limited," commercially available pressure ventilator. The generated pressure dramatically decreases above a certain inspiratory flow value (≈1 liter/sec), indicating that patient assistance may not be effective at large inspiratory flows, i.e., when large resistive pressure drop must be overcome. Such a failure in the inspiratory pressure support might have contributed to the poor patient tolerance of pressure modes reported in the past, and thus might explain the delay in the diffusion of pressure support modes.

force, P·S, from the entry to the exit of the mixing chamber of cross-sectional area S. This principle is better known as the momentum flux theorem, or Euler theorem. Contrary to jets freely expanding through the atmosphere, in confined jets tube walls necessarily limit the quantity of entrained air, forcing lateral pressure to increase by virtue of total thrust conservation (28,29). Thus, confined turbulent jets are able to generate an axial pressure gradient opposite ($P_2 - P_0 > 0$) to the gradient that would counterbalance the overall aerodynamic flow resistance (see Fig. 6).

Using momentum flux theorem or thrust conservation between the entry and the exit of the mixing chamber, the relationship between the generated pressure ($P_2$) and the inspiratory flow ($\dot{V}_2$) is

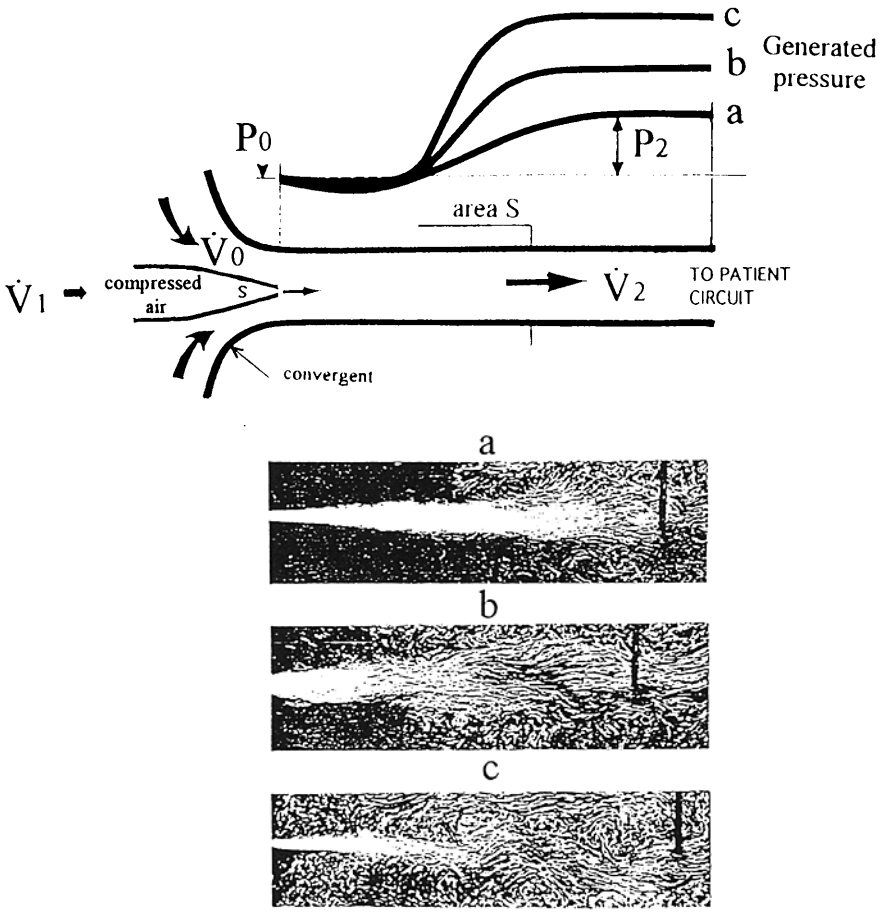



**Figure 6** The development of a turbulent jet confined in a tube whose entry is opened to the atmosphere generates an increase in lateral pressure whose detailed mechanisms are relatively complicated: eddies, visualized in panels a, b, c, resulting from mixing between the jet and entrained air, contribute to the transformation of momentum flux (flow of injected air: $\dot{V}_1$) into pressure ($P_2$) (modified from Ref. 29). Case a corresponds to large entrained flow (total flow about six times the injected flow); case b corresponds to intermediate entrained flow and total to injected flow ratio of about 3; case c corresponds to zero entrained flow (total flow equals injected flow). The turbulent confined jet provides an axial pressure increase opposed to the main flow: the higher the pressure generated by the jet mixing, the stronger the eddy production between the jet and surrounding air, and the smaller the entrained flow $\dot{V}_0$ and the inspiratory flow $\dot{V}_2$. Note that pressure $P_0$ is atmospheric in the present case.

$$\rho[(\dot{V}_2^2/S) - \dot{V}_0^2/(S-s) - \dot{V}_1^2/s] = S\,(P_0 - P_2) \quad (3)$$

where $\dot{V}_0$, $\dot{V}_1$, and $\dot{V}_2$ are, respectively, the entrained gas flow, the injected flow, and the total (inspiratory) flow, S and s are, respectively, the mixing chamber area and injector area, and $P_0$ and $P_2$ are, respectively, the pressures at entry and at exit of the mixing chamber. $P_2$ may be seen as the assistance pressure.

Fundamental studies (28,29) have shown that a distance equivalent to about 5 diameters of mixing chamber was necessary to transform the jet momentum flux into pressure for the highest values of the $\dot{V}_2/\dot{V}_1$ ratio, i.e., for large entrained flows. Equation (3) and Figure 7 show that the generated pressure inevitably decreases when inspiratory flow increases. To improve the performance of pressure generators and to approach a pressure plateau, it is necessary to minimize the slope of the pressure-flow relationship ($P_2 - \dot{V}_2$). In a recent application of such a system (11), inspiratory positive airway pressure (IPAP) was optimized using sufficiently high injected flow values in order to decrease the difference $U_2 - U_1$, upon which the ($P_2 - \dot{V}_2$) slope depends, and in reducing the tube resistance to entrained flow. This system has proven efficient in assisting patients with acute respiratory failure (11).

Systems with nonaxial turbulent jets have also been used to generate a positive pressure in the trachea of intubated patients (30). Microjets issued for

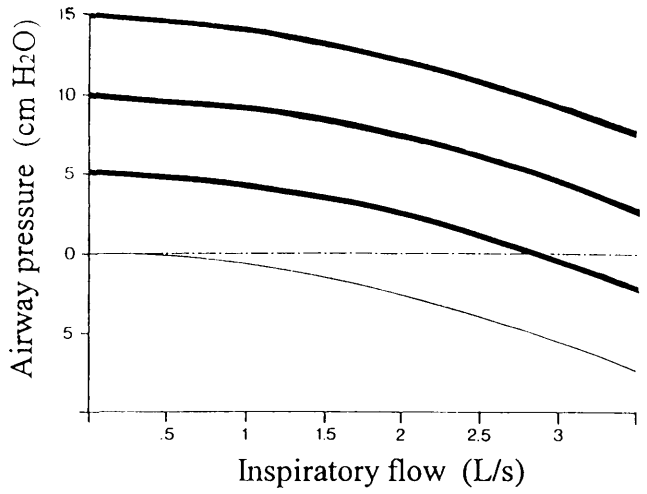



**Figure 7** Relationship between airway pressure and inspiratory flow in a confined turbulent jet system similar to the system shown in Figure 6. Note that this system is able to pressurize an unlimited quantity of air (up to 2–3 liters/sec) with only a slight decrease in airway pressure.

capillaries extruded in the wall of the endotracheal tube generate a positive pressure capable of overcoming endotracheal tube resistance and the inevitable Bernoulli effect by virtue of a mechanism similar to the one described above, except that nonaxial incidence of jets as well as friction between the jets and with the wall play a nonnegligible role. As illustrated in Figure 8, the resulting axial increase in pressure depends on the overall injected flow through capillaries and on inspiratory flow as in the axial jet. When injection occurs during the inspiratory phase only, this system can be considered as a positive pressure ventilator usable in the frequency-controlled mode or in the assist mode. However, when injection occurs throughout the entire respiratory cycle, the system behaves as a constant positive airway pressure (CPAP) device.

## III. Internal Impedance and Circuit Impedance

In 1968, Peslin (31) initiated a simple method to evaluate the mechanical performance of ventilators. He considered ventilators as ideal flow sources, or ideal

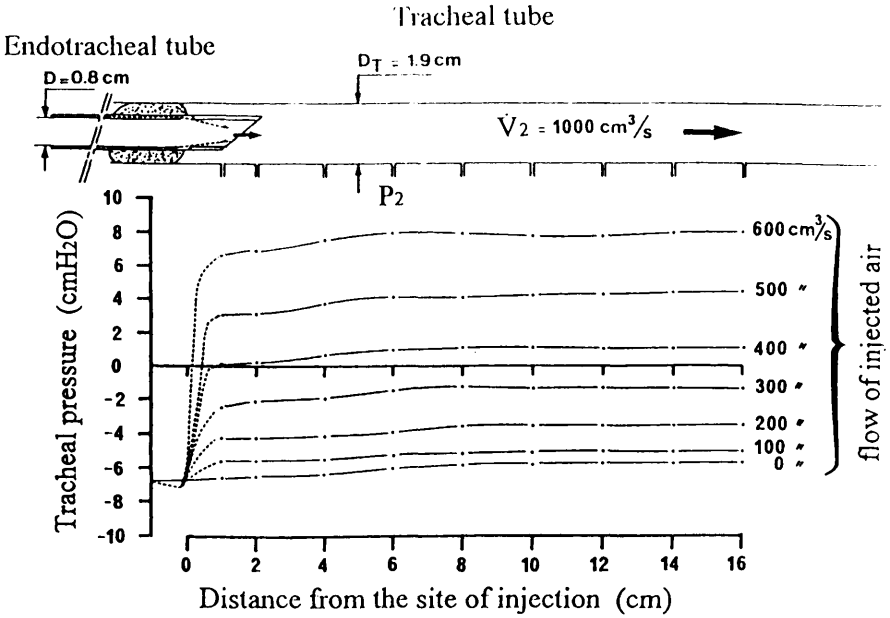



**Figure 8** Axial pressure profiles in the transition from endotracheal tube to trachea for a given inspiratory flow value ($\dot{V}_2$ = 1 liter/sec) and different injected flow values (up to $\dot{V}_1$ = 0.6 liter/sec). This system is similar to that shown in Figure 4 or 6, except that jets are not axial and may interact (see Ref. 30).

pressure sources, the performances of which were degraded by passive electrical resistance-compliance (R-C) properties of the ventilator and/or ventilator circuit. Accordingly, the magnitude of the internal resistance determined the performance in quasi-steady conditions and thus the type of ventilator, whereas the internal compliance was related to the dynamic response of the ventilator.

Based on Peslin's concept (31), a ventilator that maintains a constant flow throughout the entire inspiratory cycle, whatever the mechanical characteristics of the patient, does have an infinite internal resistance. This condition is difficult to achieve practically even using nozzles or a sonic throat as demonstrated above. Thus, ventilators in the standard flow-controlled mode (CMV) usually associate high-internal-resistance flow generators along with servo-controlled mechanisms correcting any deviation from constant flow. As a matter of fact, most sophisticated modern ventilators are flow-controlled, in which inspiratory flows predetermined in shape and in magnitude are almost unaffected by patient mechanical properties.

It might be surprising to consider that decades of improvements to ventilators have been beneficial to flow-controlled modes only (CMV). In comparison, controlled pressure and/or assisted pressure modes have not improved in performance to the same extent. Internal resistance being defined as the slope of the pressure-flow relationship (only if $(P_2 - \dot{V}_2)$ is linear), it appears that maintaining constant pressure levels at airway opening means zero slope on pressure-flow diagrams and therefore zero internal ventilator resistance. This point was not explicitly mentioned in the paper by Peslin (31) or in classical textbooks on mechanical ventilation (32). Moreover, low-internal-resistance ventilators have often been connected to low-cost ventilators with no guarantee in terms of mechanical performances. It is easy to understand how variability of performances between pressure ventilators has contributed to the negative opinion of clinicians concerning pressure modes. Another important point concerning pressure ventilators is that the inspiratory circuit acts as an external resistance and thereby contributes to the degradation of the pressure plateau generated inside the machine. By comparison, due to flow conservation, inspiratory circuits (with no leaks) are not able to degrade the flow plateau in standard controlled modes.

Considering the analogy between mechanical and electrical quantities, it can be said that pressure ventilators should be able to maintain a constant (but predetermined) level of pressure in the same way that electrical plugs deliver current at a constant voltage whatever the intensity needed (for standard apparatus). This remains a difficult task because fluid flowing in an inspiratory circuit or any tube necessarily constitutes an aerodynamic resistance, mostly flow-dependent. Moreover, ideal pressure generators do not exist for physical reasons (see above). Thus, ventilators with zero internal and external resistance require coupling optimized pressure generators, such as the turbulent confined jets described above, with a servo-controlled regulation of the pressure that is measured as close as possible to the airway opening.

In the pressure support mode, the response of pressure generators must be fast enough to reach the pressure plateau at the beginning of inspiration. Although the appropriate value required to minimize the inspiratory effort is not known, it can be assumed that the faster the rise in pressure, the higher the pressure assistance and the smaller the patient effort (6,7). However, due to gas compressibility in the inspiratory circuit, which acts as an internal compliance, the pressure rise cannot be instantaneous (31). Reduction of this compliance by minimizing the inner volume of the inspiratory line might appear desirable to improve the performance of pressure support modes. In such a case, reduction in tube length would be preferable to reduction in tube diameter, because tube resistance depends on tube diameter at power 4–5 while the dependence on tube length is much less. With the quickly responding machines presently available, a minimum of 50 msec is required to reach the inspiratory pressure plateau (lung model with compliance 0.1 liter/cm$H_2O$ and resistance 5 cm$H_2O$ at 1 liter/sec).

As far as performance of commercially available pressure ventilators is concerned, one must consider two major practical aspects. First, the mechanical properties of pressure ventilators must be evaluated with pressure and flow signals measured as close as possible to the airway opening, because the circuit connecting the ventilator to the patient imposes a resistance to gas flow. For similar reasons, the pressure evaluation must be performed with the circuit that will be used in the patient. Accordingly, interconnecting inspiratory circuit devices (e.g., one-way valves, constrictions, humidifiers), will necessarily degrade the pressure plateau simply by adding additional external resistance and compliance. Note that the earlier concept of "viscous internal resistance" proposed to characterize ventilators providing linear pressure-flow relationship has no physical meaning (31). Indeed, pressure drop in short tubes or orifices is mostly flow and density dependent, but certainly neither flow independent nor viscous dependent. Second, the performances of pressure ventilators must take into account the occurrence of leaks, especially with the recent proliferation of noninvasive ventilation via a face mask (10,11). Any leak in the inspiratory circuit makes the pressure support system work as if inspiratory flow was virtually higher. The range of flow through which pressure is maintained constant must be extended toward higher flow values in order to take leaks into account, especially in case of inspiratory assistance via a mask.

## IV. Flow and Pressure Measurements

Both the development of pressure support modes synchronized with patient inspiratory activity and the adjustment of the level of pressure support according to the mechanical characteristics of the patient require instantaneous detection and/or accurate measurement of flow and pressure at sites as close as possible to the airway opening. This requires better knowledge of basic aerodynamic princi-

ples involved in the systems used to measure pressure and flow. For instance, if gases other than air are used, it is important to know the effects of their physical properties. In addition, mucus accumulation, aerosols, and humidity may alter or even compromise measurements, and the location of the measurement apparatus may become determinant. Other factors include the ability of measurement systems to detect the onset of inspiration, i.e., their sensitivity at low flow, but also their overall resistance and dead space.

### A. Pressure Measurements

By definition, "static" pressure in a fluid is obtained by measuring the module of the stress component perpendicular to a surface parallel to the flow, i.e., zero velocity gradient in the direction perpendicular to the surface (33). To do so, a pressure probe can be introduced into the flow as long as the local velocity field is not perturbed. However, the simplest way to measure the "static" pressure in a tube is to use the tube wall to gain access to the fluid without disturbing the flow. This is why the "static" pressure in a flow is also called lateral pressure in contrast to total (lateral + dynamic) pressure measured by a probe facing the fluid stream. Fast response measurements of lateral pressure often require placing a pressure sensor at the surface of the wall in such a way that no transmission delay occurs. Low-frequency phenomena characterizing usual modes of mechanical ventilation only require a pressure tap through the tube wall. This is accomplished by drilling a small cavity in which fluid velocity is zero (dead fluid). This pressure is transmitted to the sensor, usually via a connecting tube. Pressure in a tube cross section is generally assumed to be uniform if the tube is cylindrical and of circular cross section. Note, however, that lateral pressure is not uniform within a given cross section of a nonstraight tube because velocity profiles are strongly nonsymmetrical.

Generally, lateral pressure measurement of a moving fluid is much more difficult than of a quiescent fluid (33). Errors in lateral pressure measurement are due to a variety of factors, the most important of which is the contribution of dynamic pressure to the measured pressure when the flow is not parallel to the tube wall or when the wall is irregular. The geometry of the pressure cavity is also an important factor in the precision of the lateral pressure measurement.

Concerning the geometry of the pressure tap in circular tubes, it is recommended to drill a cavity, the diameter of which is

$$\frac{d}{D} < \frac{78.6}{Re^{0.7}}$$

where d and D are, respectively, the diameter of the pressure tap and the diameter of the tube in the measurement section. *Re* is the Reynolds number in the main tube. For instance, in air and with a maximum flow of 1500 $cm^3$/sec, the diameter of the pressure tap should be less than 2 mm. The distance through which the tube

wall is drilled should not be less than 2d. Beyond this distance, a hole or a tube of larger diameter can be used for connection with the pressure port of the pressure transducer.

Special care should be taken in making orifices for pressure taps. If the direction of the pressure hole is not perpendicular to the tube wall, the error depends on the angle between the fluid velocity and the hole direction. The smaller the angle of the flow direction, the larger the error. If the pressure tap is needlelike and if the needle penetrates inside the tube at the site where the pressure is measured, thus constituting an obstacle to the flow, the measured pressure greatly underestimates the true lateral pressure, e.g., 40% of dynamic pressure for an obstacle whose height equals the tube diameter. On the other hand, if the needle constitutes a small recess in the tube wall, the measured pressure may overestimate the true lateral pressure. For a large recess, the measured pressure underestimates the true lateral pressure by only a few percentage points of dynamic pressure.

It is not the aim of this chapter to review the physical principle of pressure transducers (33), which, unlike flow transducers (34), do not involve fluid mechanics except in the vicinity of the pressure tap as described above.

### B. Flow Measurements

Flow transducers are used in mechanical ventilators as monitoring instruments or integrated to the servo-mechanism of the ventilator. Flow transducers usually involve physical models whose principle and limits of applicability must be known (34) before performing the ventilator evaluation.

#### *Laminar Flowmeters*

The classical Fleisch pneumotachograph is a laminar flowmeter. The flow is divided through a large number of capillaries (280 capillaries of about 1 mm in diameter for the Fleisch #1) in which flow is Poiseuillelike, i.e., parabolic and viscous. The pressure difference, measured in between the entry and the exit of capillaries located around the periphery of the flowmeter, is always proportional to the total flow as long as velocity profiles upstream from the flowmeter remain axisymmetrical. Pressure difference is also proportional to gas viscosity as long as the capillary Reynolds number remains sufficiently small ($<100$) to avoid entry effects in capillaries. This condition is usually verified in the range of flow through which the pneumotachograph response is given to be linear by the constructor. Because these flowmeters offer low resistance levels, are sensitive to flow direction, and are accurate down to very low flows (their sensitivity remains constant down to zero flow), Fleisch pneumotachometers can be used to detect inspiratory flow. Their frequency response, which also depends on frequency response of the connected transducer, is appropriate for standard physiological applications.

However, they are not easy to use clinically due to water vapor condensation and septic contamination in capillaries.

### *Hot Wire Flowmeter*

The hot wire flowmeter includes, in a direction transversal to the measured flow, a thin metal wire heated at constant temperature. A feeding current counterbalances the cooling effect of the flow. The square of the intensity of current necessary to maintain a constant temperature is proportional to the square root of the gas velocity of the measured flow. The hot wire anemometer allows measurements down to very low flow rates. Because its thermodynamic inertia is very small, it allows measurements of rapid velocity variations. The hot wire anemometer can be used to detect the onset of inspiratory flow with good precision (1.5%). Due to thermodynamic transfer between the wire and the flow, calibration depends on the physical properties of the gas used. Since the hot wire can be damaged by water particles, it is not recommended to use this flowmeter near a mouth opening. The hot wire flowmeter must, however, be placed near the ventilator circuit, but only to measure unidirectional flow because it is not sensitive to flow direction. The resistance offered to flow being almost negligible, it will not contribute to an increase in inner resistance of the ventilator.

### *Venturi Flowmeters, Constant or Variable Orifices*

By principle, the Venturi flowmeter is based on energy conservation at the passage of the fluid in a constricted area (Venturi tube or orifice in a thin wall). The relative decrease in lateral pressure resulting from the longitudinal acceleration (increase in kinetic energy) as the area decreases obeys the Bernoulli equation. The pressure-flow relationship in such systems is typically proportional to gas density and to the flow squared. Thus, the flow-pressure slope dramatically nears zero as the flow approaches zero. Accordingly, it is important to mention that Venturi flowmeters, like any flowmeter based on Bernoulli equation or dynamic pressure measurement, considerably decrease in sensitivity close to zero flow, whereas the measurement error is increased secondary to the extraction of the square root of flow. The practical consequence is that they cannot be recommended to detect the onset of inspiratory flow. In Venturi systems, the overall pressure drop represents between 5 and 20% of the measured pressure drop, which might be excessive in certain patients.

Incidentally, a similar argument can be used in discussing the relative advantages of flow detection over pressure detection at the beginning of inspiration. Indeed, because inspiratory circuits of most pressure support systems are opened to the atmosphere through a flow-dependent resistance, the negative pressure causing inspiratory flow has a nonlinear character: $P - Patm \sim \dot{V}^a$, with $a = 1.5$ in entry flow, $a = 1.75$ in hydraulically smooth turbulent flows, and $a = 2$ in

orifice flows. Thus, sensitivity defined as the pressure-flow slope decreases as flow tends to zero. On the contrary, laminar flowmeters exhibiting linear pressure-flow slope, or any kind of flowmeter with high sensitivity near zero flow, should constitute a better detector of inspiratory effort than pressure measurements performed in the inspiratory circuit.

#### *Ultrasound Flowmeter*

The basic principle of the ultrasound flowmeter used the change in apparent wave speed of sound propagation generated by a source of ultrasounds. The change in speed, related to fluid velocity, is detected by a fix receptor. Application to gases is relatively recent. An even more recent development consists of comparing the time required for the sound to propagate in opposite directions, according to a direction oblique to the measured flow (transit-time method). Ultrasounds flowmeters are 1–2% accurate with a fast dynamic response. They are sometimes used in ventilators.

#### *Fluidic Flowmeters*

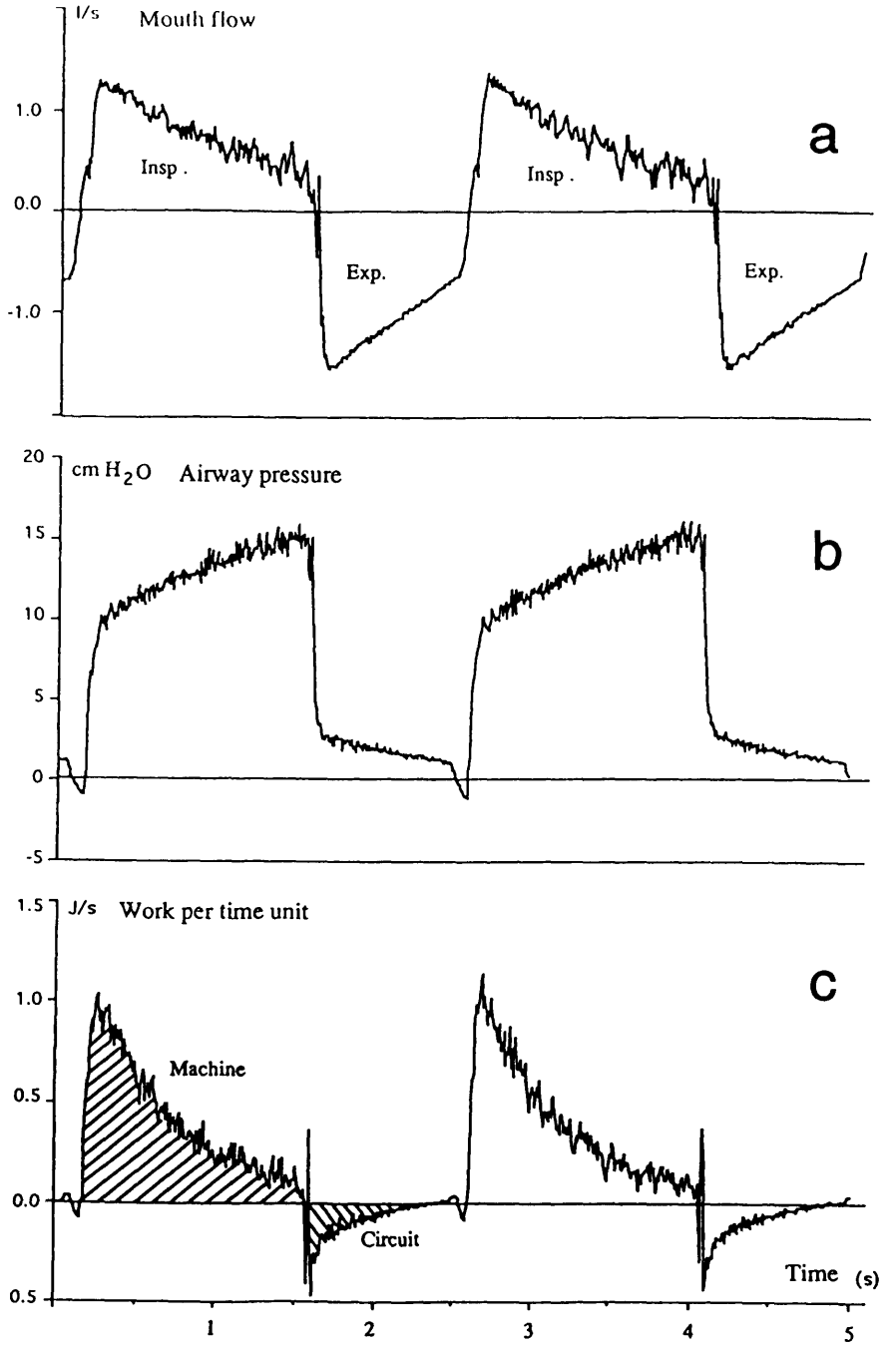
Fluidic flowmeters involve different techniques, one of which uses metallic pieces vibrating at a frequency proportional to the fluid velocity. The resulting motion is converted into an alternative tension by means of an electromagnetic system.

Another kind of fluidic system consists of using the frequency of swirls generated downstream from a bar or an obstacle placed transversally to the measured flow. The frequency of swirling detachment, which is proportional to the fluid velocity, can be measured by thermal transducers, force transducers, or oscillating beads. These flowmeters are only slightly sensitive to temperature variations, humidity, or water vapor condensation. Their linearity range depends on their Reynolds number. Their response depends on the gas density. To our knowledge, fluidic flowmeters are rarely used in clinics, although they have potential advantages, taking into account the wide variety conditions of applications.

In summary, to perform flow measurements in the vicinity of mouth openings and in the course of pressure support, criteria such as low deadspace, low resistance, fast response, or insensibility to water or humidity should be considered when selecting flowmeters.

## V. Evaluation of Ventilators and Ventilatory Modes

Ventilator evaluation differs between the controlled mode and assist mode. Controlled modes (CMV) can be evaluated from pressure-flow diagrams established as recommended by Peslin (31). The experimental set-up consists of a passive


l/s
Mouth flow
1.0
0.0
-1.0
Insp .
Exp.
Insp .
Exp.
a
20
cm $H_2O$
Airway pressure
15
10
5
0
-5
b
1.5
J/s
Work per time unit
1.0
0.5
0.0
0.5
Machine
Circuit
c
Time (s)
1
2
3
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5

mechanical circuit made of a resistance placed at the outlet and gradually varied while the pressure at the inlet of the resistance and the flow rate are measured simultaneously, following the recommendations given above. The performance of ventilators in the flow-controlled mode can be evaluated in the constant flow mode, where the quality of the flow plateau is relatively easy to determine under various conditions of airway pressure ($< 100$ $cmH_2O$). On the other hand, estimation of the performance of a pressure-controlled mode can be performed by studying the effect of increasing inspiratory flow (using a pump or a vacuum producing flows ranging from 0 to 1.5–2 liters/sec) on the pressure created by the tested ventilator.

To evaluate the performance of pressure assist modes, the above-described passive set-up is not appropriate. It is necessary to simulate the inspiratory effort of the patient. The simplest way to do this is to use a lung model in which a repeatable inspiratory effort can be initiated and eventually maintained throughout inspiration or during a part of it, whereas the tested machine freely contributes to the other part of the ventilation, depending on the level and type of assisted breathing (IPS, PAV). Such active lung models are not yet commercially available, but simulation of the inspiratory effort can be achieved with a two-compartment lung model (35), where one lung compartment, connected to a flow-controlled ventilator (CMV ventilator), lifts up the second lung compartment by means of a small metal insert. This second compartment is connected to the tested pressure support machine, which provides a complementary insufflation, depending on the level of pressure support. It can always be freely insufflated by the pressure support device, whatever the initial displacement caused by the first compartment.

Typical signals obtained in such a lung model are presented in Figure 9 for an IPS machine designed to provide noninvasive pressure assistance in the ICU (11). The predetermined parameters are as follows:

The level of pressure assistance usually defined by the maximum pressure obtained at the end of inspiration. The standard range in 8–20 $cmH_2O$.

The inspiratory flow values at which pressure assistance is started and then stopped. There are a variety of criteria to detect the onset of inspiration.

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**Figure 9** Experimental test of pressure support ventilation: (a) mouth flow, (b) airway pressure, and (c) work per time unit at the entry of an active lung test model (two compartments), with one compartment connected to the tested inspiratory pressure support device. In this case, a system designed for the ICU was tested (ARM 25, TAEMA, France). Frequency and inspiratory flow levels fixed by the "patient" are set on the CMV ventilator, which is connected to the other compartment. Note that negative pressure at onset of inspiration is minimized, suggesting that patient inspiratory effort is minimized. Moreover, maximum flow and work performed by the tested pressure support machine are maximal at the beginning of inspiration and then decrease due to airway pressure–inspiratory flow relationships resembling the curves shown in Figure 7.

Some are based on flow signal—a minimal inspiratory flow is detected, e.g., 1 liter/min as in the IPS machine used in the example in Figure 9. Others are based on pressure measured somewhere in the inspiratory circuit. It is usually recommended to stop inspiratory pressure support at a flow level about 25% of maximum flow, as shown in Figure 9.

The breathing frequency of the patient, the flow or tidal volume generated by the "patient" model.

The following parameters can be obtained from the analysis of data such as those in Figure 9:

The minimal value of airway pressure at the onset of inspiration and the time to reach this value.

The work performed by the tested machine and eventually the work performed by the patient during inspiration. These quantities are estimated by reference to the mechanical properties of the passive system.

The mean value of expiratory pressure, the positive end expiratory pressure (PEEP) imposed by the setting, and the work imposed by the expiratory circuit to the patient.

The quality of the "pressure plateau."

The time required to reach maximum inspiratory flow.

To compare pressure support ventilators and modes (6,7,10,11), pertinent criteria are (1) maximal sensitivity of the detection (i.e., negative pressure and time to reach this value at onset of inspiration have to be minimal), (2) "plateau" of pressure support, estimated by the mean to maximum pressure ratio (assuming the lung is a simple R-C system, this criterion means that maximal inspiratory flow must be reached in a time as short as possible), (3) a major part of the work of breathing is performed by the machine during inspiration with a minimal contribution of the patient in terms of inspiratory effort, (4) minimal mean expiratory pressure, i.e., minimal resistance of the expiratory circuit.

In summary, there has been considerable improvement in ventilator technology in recent years. Most ventilators are now able to generate flow/volume modes with acceptable characteristics. However, there is still considerable diversity in the quality of the performances of ventilators in the different pressure modes. The physician should therefore carefully check the characteristics of the ventilator before using it in patients, especially in the pressure support mode, which is now widely applied during the period of weaning from mechanical ventilation.

Having performed this evaluation procedure, the physician must still ask: What is the optimal pressure pattern? Until now, this question could not have been addressed simply, due to the unreliability of ventilators, which were not able to provide the pattern to be tested in every situation, including the ventilation of patients with high airway resistance, low compliance, and/or high inspiratory flow

rates. There is some evidence that, depending on the pathology, different assist ventilation modes can be used, especially if the evolution of mechanical properties and physiological data are taken into account. Future ventilators might also include a regular adjustment of the ventilatory mode. To take into account the evolution of mechanical and physiological parameters as well as therapeutic strategies, new tools of control such as artificial intelligence have recently aroused particular interest (22).

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# 28

# Mechanical Ventilation in the Passive Patient

## Theory and Clinical Investigation

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## I. Introduction

A "passive" or relaxed patient is a patient without discernible spontaneous activity of the respiratory muscles during ventilatory assistance, in whom mechanical ventilation is delivered in the control mode, i.e., controlled mechanical ventilation (CMV) (1). The difference between CMV and other modes of ventilatory assistance, such as assist/control mechanical ventilation (AMV), synchronized intermittent mandatory ventilation (SIMV), pressure support ventilation (PSV), and, more recently, proportional assist ventilation (PAV) is that with CMV the pressure required to inflate the patient's respiratory system is entirely provided by the ventilator (2). In contrast, with the other modes of ventilatory assistance, the patient's inspiratory muscles must contract to trigger the mechanical breath (2). This activity does not cease with the start of the mechanical lung inflation, but may proceed well into inspiration (3). Indeed, in some instances, the work done by the patients' respiratory muscles during AMV may be as great as during unassisted breathing (3). CMV is frequently needed during the first days of mechanical ventilation to rest the patients' respiratory muscles as well as to ensure full control of alveolar ventilation and arterial blood gases. CMV is necessary if the patient presents one or more of the following conditions:

1. Insufficient neuromuscular drive to breathe, due either to abnormally low respiratory center activity or inspiratory muscle weakness or fatigue.
2. Low cardiorespiratory reserve, such that even a small levels of work of breathing may not be tolerated.
3. Poor coordination of respiratory muscle activity, which can prevent adequate control of alveolar ventilation, arterial blood gases, and cardiorespiratory function.

In some instances, sudden distress may appear in a previously stable patient for a variety of causes, which need to be carefully investigated. At times, adjustment of the ventilator setting plus administration of analgesic and sedatives may be required (2). Even muscle paralysis may be needed. In the latter case, the duration of neuromuscolar blockade must be kept as short as possible not only to prevent the danger of accidental disconnection from the ventilator, but also to avoid prolonged respiratory muscle weakness after the discontinuation of those agents (4).

Patients with acute respiratory failure (ARF) due to exacerbation of chronic obstructive pulmonary disease (COPD) are often agitated because of severe dyspnea. They also breathe rapidly and shallowly because of irritant and J-receptor stimulation and/or impending or actual respiratory muscle fatigue (5,6). Critically ill COPD patients may have very low cardiorespiratory reserve due to excessive pulmonary hyperinflation, hypoxia, respiratory acidosis, and impaired cardiac function. Under such circumstances, CMV represents the only way to rest the respiratory muscles and to improve arterial blood gases and pH. Sedation and muscle paralysis are at times needed to obtain a satisfactory adaptation of the patients to the imposed ventilatory pattern. In general, after a few days on CMV, COPD patients are assisted with either AMV, SIMV, or PSV (7), often associated with some level of positive end-expiratory pressure (PEEP) (8), and eventually with continuous positive airway pressure (CPAP) for weaning (9). In this chapter only CMV will be discussed.

## II. Controlled Mechanical Ventilation and Respiratory Mechanics

In addition to ventilatory assistance, CMV provides an unique opportunity to assess the mechanical properties of the patient's respiratory system and obtain a better understanding of the pathophysiological changes associated with acute exacerbation of COPD. During CMV, the respiratory muscles are essentially relaxed and the upper airway is bypassed by the endotracheal tube (Ett). Under these conditions, the use of simple and commonly available equipment such as a pneumotachograph to measure flow and volume, by either electrical or numerical

integration, and a differential pressure transducer to measure pressure at either the proximal (Pao, pressure at the airway opening) or distal (Ptr, tracheal pressure) tip of the endotracheal tube, provides useful information about patients' respiratory mechanics, which is used to assess the status and progress of the disease as well as the effects of treatment. In this chapter we will review some recent advances in our knowledge of respiratory mechanics in mechanically ventilated COPD patients and will discuss their clinical implications. A series of studies on normal anesthetized subjects (10–12) has provided useful data for comparison of respiratory mechanics with those of mechanically ventilated COPD patients.

In the last 10 years, some traditional but not widely used techniques to measure respiratory mechanics have been reevaluated and adapted to mechanically ventilated patients (e.g., the interrupter technique), and new techniques have been developed as well. These techniques have some common features: (1) all can be noninvasive, (2) measurements can be performed at the bedside, and (3) all are suitable for computer processing.

In the passive patient, changes in lung volume depend on externally applied pressure. The respiratory system can be inflated by applying either a negative pressure around the chest wall (or the whole body excluding the head) or a positive pressure at the airway opening. The former, i.e., intermittent negative pressure ventilation (INPV), has been extensively used in patients with neuromuscular disorders, particularly during the polio epidemics of the early 1950s, and only occasionally in patients with acute exacerbation of COPD (13–15). By contrast, intermittent positive pressure ventilation (IPPV) has become the most widely used method of mechanical ventilatory assistance in the intensive care unit (ICU). To our knowledge, IPPV in the CMV mode has not been applied in patients with acute exacerbation of COPD without endotracheal intubation. Therefore, in this chapter, "passive" patients receiving CMV will be assumed to have an endotracheal tube bypassing the upper airway.

CMV can be delivered by volume-cycled or pressure-cycled ventilators. In both instances the mechanical ventilator will generate a positive pressure at the airway opening to inflate the respiratory system. When volume is the primary variable (volume-cycled ventilators), the ventilator will deliver the amount of pressure needed to achieve the preset volume independent of the mechanical properties of the patient's respiratory system. This is the traditional CMV. When pressure is the primary variable (pressure-cycled ventilators), the ventilator will deliver the preset pressure, and volume will depend on the patient's respiratory mechanics. This kind of mechanical ventilation is termed pressure-controlled ventilation (PCV) and has not been used as yet in COPD patients with ARF.

During CMV, all ventilatory parameters are set by the ventilator: minute ventilation ($\dot{V}E$), ventilatory frequency (f), tidal volume (VT), and inspiratory (TI), expiratory (TE), and total cycle (TT) duration, as well as the duty cycle [either inspiratory time/total breathing cycle duration (TI/TT) or the inspiratory-

to-expiratory (I-E) ration]. With some ventilators (e.g., MA-1, Bear 1 and 2, PB-7200) the physicians set VT, f, and peak inspiratory flow rate ($\dot{V}I$), which determines TI, such that $\dot{V}E$ and I-E will be secondarily determined. With other ventilators (e.g., Servo 900-C), $\dot{V}E$, f, and TI/TT are the set variables that determine VT and $\dot{V}I$. A short end-inspiratory pause (<0.4 sec) is often included in TI in order to improve pulmonary gas exchange (16).

The traditional guidelines for ventilatory settings in the ICU have been derived mostly from anesthetic practice, VT being commonly set at 10–15 ml/kg of body weight and $\dot{V}E$ to maintain arterial $P_{CO_2} < 45$ mmHg (17). The choice of TI/TT or I:E is more empirical, though the most common pattern is about 1 second for inspiration, followed by 2–4 seconds for expiration, giving respiratory frequencies in the range 12–20 breaths per minute (1). Furthermore, it is a widely accepted rule to avoid excessive levels (>60 $cmH_2O$) of peak inflation airway pressure (Ppeak) (1,17). In general, this kind of setting is associated with relatively large VT (up to 0.8–1 L) (2,18). Until recently, in patients with ARF due to acute exacerbation of COPD, the use of large VT was encouraged in view of the general notion that such patients have an increased physiological dead space (VD), which is responsible for $CO_2$ retention (17,19). Indeed, with a large VD, only a large VT can provide an adequate alveolar ventilation and hence an acceptable $Paco_2$, as indicated by the following equation:

$$Paco_2 = \dot{V}co_2 \times \frac{K}{\dot{V}E(1 - VD/VT)} \quad (1)$$

where $\dot{V}co_2$ is the $CO_2$ production, K is constant, and $\dot{V}E(1 - VD/VT)$ is alveolar ventilation ($\dot{V}A$). However, in patients with exacerbation of COPD, the use of large VT can determine incomplete lung emptying and hence contribute to dynamic pulmonary hyperinflation (18,20–24).

## III. Pulmonary Hyperinflation

The functional residual capacity (FRC) is defined as the amount of gas in the lungs and airways at the end of spontaneous expiration (25). Under normal conditions, and also in some pulmonary diseases (e.g., alveolitis, interstitial fibrosis), the elastic energy stored in the respiratory system during the preceding inspiration is sufficient to complete expiration in the time available between inspirations. FRC is then determined by the balance between the opposing elastic forces of the lungs and chest wall and corresponds to the elastic equilibrium volume of the total respiratory system (Vr) (26). Under these circumstances, the end-expiratory flow becomes nil before the onset of the next inspiration (or mechanical lung inflation), as indicated by the presence of an appreciable end-expiratory pause (Fig. 1). *Pulmonary hyperinflation* is defined as an increase of FRC above predicted values.

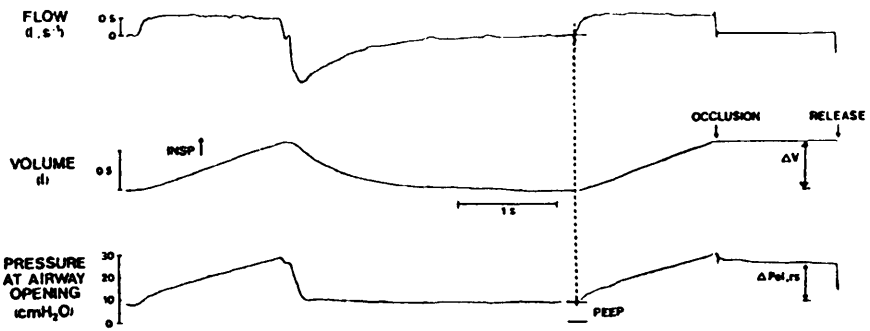


**Figure 1** Tracings of flow, volume, and pressure at airway opening in a mechanically ventilated surgical patient with acute respiratory failure. In this subject expiratory flow became nil before the end of the expiration, and inspiration flow started synchronously with the onset of positive pressure inflation as indicated by the vertical dashed line with PEEP of 10 $cmH_2O$.

It has long been recognized that pulmonary hyperinflation is a hallmark of advanced COPD (27). In patients with stable COPD, pulmonary hyperinflation is mainly due to loss of lung elastic recoil and closure of small airways (air trapping). Chest wall mechanics remain essentially normal (27). Dynamic pulmonary hyperinflation (DPH) is defined by an increase in FRC above Vr due to the presence of dynamic factors: (1) increased magnitude and duration in the postinspiratory muscle activity, (2) airway constriction, (3) large tidal volume, and (4) short expiratory duration (26,28). During CMV, the respiratory muscle are normally relaxed and hence there is no postinspiratory activity. The expiratory duration is set by the ventilator and, hence, theoretically could be adjusted to allow complete expiration. In practice, however, this is not the case. Indeed, it has been shown that in most mechanically ventilated patients with acute exacerbation of COPD, even a TE of 20–30 seconds may not be sufficient to deflate the lungs to Vr (18,20). However, the most common cause of DPH in mechanically ventilated patients with acute exacerbation of COPD is by far the abnormal increase in airway resistance associated with expiratory flow limitation. The latter is the consequence of dynamic compression of the airways during expiration. Because the time needed to decompress the lungs to Vr is too long, expiration cannot be completed with the TEs commonly used, and flow is present at end expiration, being curtailed only by the onset of the next mechanical lung inflation. As shown in Figure 2, the end-expiratory pause is replaced by a sudden reversal of expiratory to inspiratory flow. In this case, the end-expiratory lung volume (EELV) during mechanical ventilation exceeds Vr, i.e., DPH occurs. In patients with acute exacerbation of

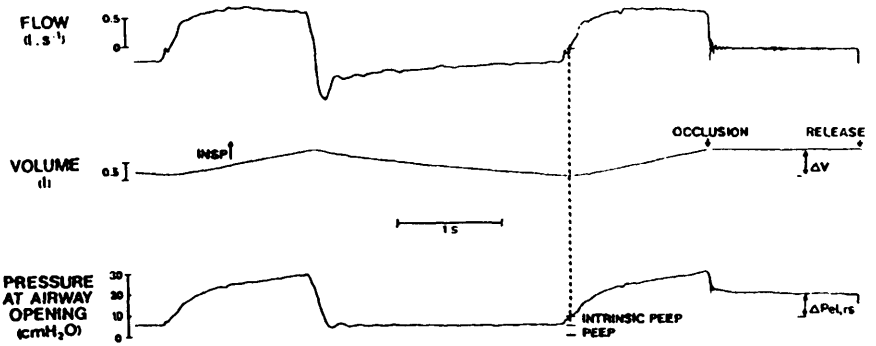


**Figure 2** Tracings of low, volume, and pressure at airway opening in a mechanically ventilated COPD patient with PEEP of 5.5 $cmH_2O$. In this patient expiratory flow continues throughout expiration, and the end-expiratory pause is replaced by a sudden reverse of flow from expiration to inspiration. Also note that in this patient inspiratory flow starts only after a pressure change of +4.5 $cmH_2O$ is applied by the ventilator, as indicated by the vertical dashed line. This pressure is required to overcome the end-expiratory elastic recoil and is termed dynamic intrinsic PEEP.

COPD and status asthmaticus (29–31) there may be a marked degree of dynamic pulmonary hyperinflation.

### A. Expiratory Flow Limitation

COPD is characterized by reduced maximum expiratory flows. The maximum flow-volume envelope is considerably reduced, and expiratory flow limitation may occur at moderate levels of ventilation or even during resting breathing (17,25). During ARF, probably because of exacerbation of the inflammatory process in the bronchial walls as well as smooth muscle contraction, tidal expiratory flows are maximal (20,23,32). In mechanically ventilated COPD patients, the presence of expiratory flow limitation is *suggested* by (1) a transient flow "spike" at the onset of expiration (Fig. 2) (31) and (2) a convexity toward the volume axis of the expiratory flow-volume curve (Fig. 3) and is *confirmed* by (3) analysis of isovolume pressure-flow curves (20,32,33), as well as (4) lack of change in expiratory flow-volume curve with application (23) and/or removal of added resistance (33), as well as of positive (Fig. 3) or negative pressure at the airway opening (33). The latter is in line with the waterfall theory of expiratory flow limitation: changes in resistance and/or pressure downstream of the equal pressure point do not affect upstream resistance and driving pressure, and hence expiratory, flows until a critical value is reached (34,35). As illustrated in Figure 3, a simple technique to assess the presence of expiratory flow limitation at the bedside is the

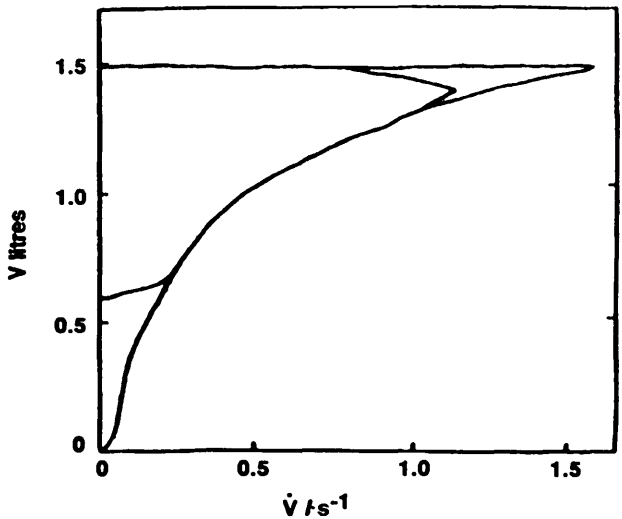


**Figure 3** Relaxed expiratory volume/flow curves in a mechanically ventilated chronic obstructive disease patient with positive end-expiratory pressure (PEEP) of 4 $cmH_2O$ (smaller loop) and without PEEP (outer loop). With 4 $cmH_2O$ of PEEP, the intrinsic PEEP was 7.5 $cmH_2O$. During expiration with PEEP of 4 $cmH_2O$, the volume/flow loop exhibited a characteristic "truncated" appearance due to the onset of the next mechanical inflation before expiration could be completed, i.e., the patient was dynamically hyperinflated. Complete relaxed expiration against atmospheric pressure resulted in a reduction of the end-expiratory lung volume, but during most of expiration the rate of lung emptying was unchanged due to preexisting dynamic expiratory flow limitation, such that removal of PEEP did not affect the effective expiratory driving pressure.

recording of relaxed expiration through the expiratory circuit of the ventilator and without the expiratory circuit, i.e., directly to atmosphere. Expiratory flow limitation is evidenced by the lack of increase in flow while expiring to atmosphere despite the elimination of the substantial resistance due to the expiratory line of the ventilator (33). Alternatively, a small amount of negative pressure (e.g., $-5$ $cmH_2O$) can be applied at the airway opening (33).

Detection of expiratory flow limitation during tidal expiration has important clinical implications. First, as previously discussed, expiratory flow limitation is associated with abnormally low expiratory flows, which promote dynamic pulmonary hyperinflation. Second, in the presence of flow limitation, expiratory flows cannot be augmented by increasing the driving pressure, e.g., applying a negative pressure at the airway opening or by means of external compression of the chest wall during expiration. Finally, as will be further discussed below,

because of expiratory flow limitation, moderate levels of PEEP can be applied in mechanically ventilated COPD patients without increasing lung volume.

### B. Intrinsic PEEP

If an end-expiratory pause, i.e., zero flow, can be detected toward end-expiration (Fig. 1), EELV corresponds to Vr, and the end-expiratory alveolar pressure is atmospheric [zero end-expiratory pressure (ZEEP)] or equal to the level of PEEP set by the ventilator. In contrast, when the end-expiratory pause is replaced by a sudden change of the end-expiratory flow profile from expiration to inspiration (Fig. 2), dynamic pulmonary hyperinflation is present. In this case, without PEEP being set by the ventilator, the alveolar pressure remains positive throughout the breathing cycle because of persistent positive elastic recoil of the respiratory system. The end-expiratory elastic recoil pressure (Pst,rs) has been termed intrinsic positive end-expiratory pressure (PEEPi) (22) or "occult" PEEP or auto-PEEP (21,36).

The clinical implications of PEEPi in mechanically ventilated patients have been extensively reviewed elsewhere (36,37) and are further discussed in other chapters of this book. The most important clinical consequence of PEEPi is the increase in the patient's energy cost of breathing during both assisted mechanical ventilation and weaning, an aspect that is not relevant for the "passive" patient. Nevertheless, PEEPi also has important implications during CMV, such as impairment of cardiac function and increased risk of barotrauma (38), similar to excessive PEEP set by the ventilator. Unrecognized PEEPi can lead to misinterpretation of hemodynamics data, e.g., systemic hypotension, causing erroneous interpretation of a patient's volemic status (21). The patient can be overloaded with fluid, while changes in the ventilatory setting and bronchodilatation would be more appropriate. An interesting clinical observation has been reported by Conti et al. (39) in a mechanically ventilated COPD patient in whom an isorhythmic atrioventricular dissociation was coupled with dynamic pulmonary hyperinflation (PEEPi = 17 $cmH_2O$) during intermittent mandatory ventilation (IMV). The cardiac arrhythmia was successfully reversed by switching from IMV to pressure support ventilation, which, by decreasing the respiratory rate, reduced PEEPi to 7 $cmH_2O$.

Unrecognized PEEPi can introduce important errors in the computation of static respiratory compliance (Cst,rs) (22). This point will be dealt with later in this chapter.

As previously discussed, increased flow resistance, short expiratory duration, and large tidal volume can elicit dynamic pulmonary hyperinflation and PEEPi. Another factor that promotes PEEPi is the end-inspiratory pause (in general $< 0.4$ sec), which is commonly used in the ICU to improve gas exchange (16). It should be noted, however, that the end-inspiratory pause causes not only an

increase in the inspiratory time, and hence a decrease in TE for a given frequency, but also a decrease in the pressure available to produce expiratory flow, as will be discussed in greater detail in the next section.

Table 1 provides the values of dynamic pulmonary hyperinflation and PEEPi obtained by different authors in mechanically ventilated patients with acute exacerbation of COPD. Figure 4 illustrates the volume-pressure relationship of a mechanically ventilated COPD patient with ARF who has both dynamic pulmonary hyperinflation and PEEPi.

Because of its many consequences in the clinical settings, measurement of PEEPi should be performed routinely. In the "passive" patient, such measurement can be easily obtained at the bedside with noninvasive techniques that are suitable for monitoring and computer processing. First, PEEPi should be suspected whenever the end-expiratory pause in the flow record is replaced by a sudden flow reversal with the onset of mechanical inflation (Figs. 2 and 3). Then PEEPi can be measured by means of two methods, which can also be used in association: (1) by continuous recording of flow and pressure at the airway opening (22) (Fig. 2) and (2) by end-expiratory airway occlusion (EEO) long enough to reach a plateau in pressure to determine the end-expiratory Pst,rs (>1 and <5 sec) (10,21,44) (Fig. 5).

Airway occlusion at end-expiration can be accomplished in several ways. The simplest is the use of the end-expiratory hold button present in some ventilators (e.g., Servo 900C). With other ventilators that do not include this options, airway occlusion may be performed using different techniques, which provide identical results (45,46).

Measurement of intrinsic PEEP can also be obtained with a modification of the supersyringe technique. The supersyringe has been used extensively to measure respiratory mechanics in mechanically ventilated ARDS patients (47,48), though the results involved artefacts due to oxygen consumption during the long

**Table 1** Values of PEEPi and DPH in COPD Patients During CMV

| No. of patients | PEEPi ($cmH_2O$) | $\Delta FRC^a$ (L) | Ref. |
|---|---|---|---|
| 8 | 13.6 ± 6.7 | 0.66 ± 0.02 | (18) |
| 11 | 5.1 ± 0.3 | — | (24) |
| 6 | 4.6 ± 0.9 | 0.42 ± 0.18 | (40) |
| 6 | 7.3 ± 2.2 | 0.60 ± 0.46 | (41) |
| 9 | 9.8 ± 0.5 | 0.91 ± 0.99 | (42) |
| 10 | 5.7 ± 0.9 | 0.34 ± 0.06 | (43) |

[a]ΔFRC represents the difference between Vr and EELV during stable mechanical ventilation, as illustrated in Figures 3 and 4.

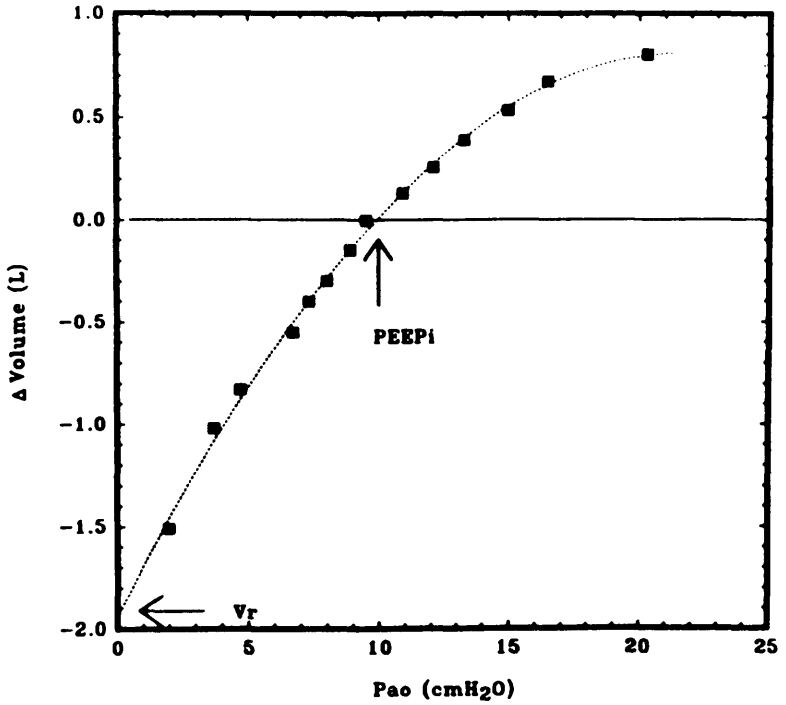


**Figure 4** Volume-pressure relationship in a mechanically ventilated patient with acute exacerbation of COPD during controlled mechanical ventilation. Pressure was measured at the airway opening (Pao). The interrupter technique was used throughout a complete relaxed expiration. Squares are measurements from multiple interruptions. Dotted line has been extrapolated to the intercept on the y axis: the difference between Vr and ΔVolume = 0 estimates the amount of dynamic pulmonary hyperinflation (>1.5 L in this patient). The value of Pao at ΔVolume = 0 reflects the amount of the intrinsic PEEP (about 10 $cmH_2O$ in this patient).

experimental procedure (49–51). In mechanically ventilated patients with COPD, the supersyringe, connected to a microcomputer controlled valve for airway occlusion, has been used for automated measurement of intrinsic PEEP (51,52). Similar to the three-way valve (50,51), the automated supersyringe method also yielded values of PEEPi essentially identical to those obtained with the Servo 900C end-expiratory hold button (50,52). Measurement of PEEPi is needed to obtain the correct value of respiratory compliance (or its reciprocal elastance) (22,53).

With continuous recording of flow and pressure at the airway opening,

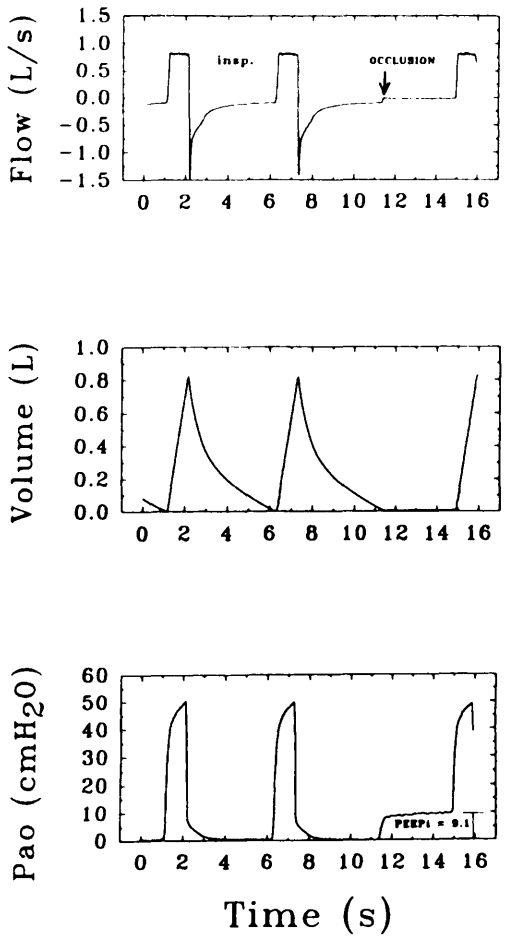


**Figure 5** Representative record with measurement of intrinsic PEEP by means of end-expiratory airway occlusion (EEO) in a mechanically ventilated patient with acute exacerbation of COPD during controlled mechanical ventilation with constant inspiratory flow. From top to bottom: records of flow, volume, and pressure at the airway opening (Pao). At the end of the second tidal expiration, the expiratory circuit of the 900C Siemens ventilator is occluded using the end-expiratory hold button of the ventilator and Pao becomes positive, reflecting the end-expiratory elastic recoil of the respiratory system due to incomplete expiration. The value of intrinsic PEEP is provided by the difference between the EEO Pao plateau and atmospheric pressure. Visual detection of the plateau on Pao provides direct evidence of (1) absence of leaks in the circuit, (2) respiratory muscle relaxation, and (3) equilibration between alveolar and tracheal pressure.

PEEPi is measured in terms of positive pressure deflection preceding onset of inspiratory flow. Henceforth, PEEPi obtained with this method will be referred to as dynamic intrinsic PEEP (PEEPi,dyn) (Fig. 2). Although in one study (22) the end-expiratory occlusion method and the ΔPao method yielded similar results, more recent reports found that PEEPi measured by means of EEO was significantly greater than PEEPi,dyn (9,54). PEEPi measured by means of EEO reflects the overall static end-expiratory Pst,rs, whereas PEEPi measured under dynamic conditions reflects the minimum "dynamic" PEEPi. Indeed, because of time constant ($\tau$) inequality between lung units, PEEPi cannot be homogeneously distributed in the lungs of COPD patients. PEEPi will be greater in the units with long $\tau$ and hence slow rate of emptying than in units with short $\tau$ and fast emptying. Under dynamic conditions, the long $\tau$ units are still emptying while the fast $\tau$ units may be filling, such that the change in Pao (or Ptr) preceding the onset of inspiratory flow reflects the amount of pressure required to counterbalance PEEPi in the fast $\tau$ units with the lowest level of PEEPi in order to start their filling. In contrast, during the end-expiratory airway occlusion, there is time for equilibration between lung units with different $\tau$ and different regional PEEPi, such that PEEPi measured as shown in Figure 5 reflects the average PEEPi, i.e., the total respiratory system end-expiratory Pst,rs. At lung volumes up to 60% of the predicted TLC, PEEPi is mainly due to the end-expiratory elastic recoil of the lung, since at the corresponding lung volumes the elastic recoil of the chest wall is in the opposite direction and will tend to reduce PEEPi. With FRC $>$ 60% of predicted TLC, as it is often the case in patients with acute exacerbation of COPD who exhibit dynamic pulmonary hyperinflation, the inward elastic recoil of the chest wall adds to that of the lung and hence contributes to the PEEPi of the total respiratory system (41,42,55).

## IV. Mechanical Inflation

To start inspiration the pressure applied by the ventilator must first offset PEEPi, which represents an *inspiratory threshold load* (22). During assisted ventilation and spontaneous breathing (weaning), PEEPi is a load to the patient's inspiratory muscles, which at times may be substantial. During CMV, PEEPi is counterbalanced by the positive pressure applied by the ventilator. After PEEPi has been counterbalanced, the pressure applied by the ventilator (Pappl) will overcome the opposing elastic (Pel) and resistive (Pres) forces to produce inspiratory flow and volume, according to the equation of motion:

$$\text{Pappl} = \text{PEEPi} + \text{Pel} + \text{Pres} \quad (2)$$

The simplest model of the "passive" total respiratory system is the single compartment model, in which a balloon, representing the elastic elements (alveoli,

lung parenchyma, and chest wall) is at the end of a rigid pipe representing the conducting airway. The single compartment model is characterized by a single elastance (E = Pel/VT) and a single resistance (R = Pres/$\dot{V}$), such that Eq. (2) can be rewritten as follows:

$$Pappl(t) = PEEPi + [Ers \cdot V(t)] + [RT \cdot \dot{V}(t)] \quad (3)$$

where Ers is the total respiratory system elastance (the reciprocal of compliance), RT is that flow resistance (patient's respiratory resistance plus added resistance), and V and $\dot{V}$ are inflation volume and flow at any time (t). In general, the ventilator tubings are rather stiff, such that the only opposing elastic force is the elastic recoil of the respiratory system (Pst,rs), and hence Ers accounts for the total system's elastance. In contrast, the endotracheal tube (Ett) and the ventilator tubings, circuits, and other devices offer a significant flow resistance, which is in general an important component of the total flow resistance.

Among other factors, e.g., patient's respiratory mechanics and ventilatory settings, the pressure-time profile of the applied positive pressure wave will depend on the inspiratory flow waveform (i.e., constant, sinusoidal, decelerating, etc.) (1). These options of flow waveform option, which are available in most modern ventilators, were introduced with the purpose of improving gas exchange in the lungs with severe $\tau$ inhomogeneity. However, some recent data suggest that the inspiratory flow waveform may not influence substantially the arterial blood gases (56,57). In this chapter we will focus on constant flow lung inflation, because it is the most commonly used and also because most measurements of respiratory mechanics in mechanically ventilated patients have been done with this inspiratory waveform.

When older ventilators (e.g., the Bennet MA-1 and the Bear 1) were used in the "constant inflation flow" mode, the inspiratory flow actually approached a constant value only after about a third of the inspiratory time had elapsed (Figs. 1, 2) (58). With modern ventilators (e.g., the Siemens 900C and Puritan-Bennet 7200) the inspiratory flow becomes constant earlier in inspiration, but it still does not represent the ideal "square wave." It has been shown that after the inspiratory flow has become constant, in normal subjects and in many patients, volume and pressure increase approximately linearly with time, and the rate of change in the pressure applied by the ventilator is linearly related to Ers (58,59). Indeed, as predicted by Bates and colleagues (60) by model analysis, such behavior is expected not only in normal lungs with little or no $\tau$ inhomogeneity, but also in diseased lungs with large time constant inhomogeneity. Indeed, in the presence of $\tau$ inhomogeneity, a linear relationship between pressure and volume may still exist, but it occurs only under steady-state conditions, i.e., when the flow to each compartment of the lungs becomes constant. Moreover, during the initial part of constant flow inflation, there is a progressive increase in airway pressure, which reflects redistribution of flow between units with different $\tau$. After that transient

change in pressure, i.e., during the steady-state period, the pressure applied by the ventilator and the inflation volume increase linearly with time, regardless of the complexity of the lung $\tau$ inhomogeneity. The pressure-over-time profile during constant flow inflation reflects the pressure-volume relationship (61). Under these conditions, simple inspection of the applied Pao waveform (Fig. 6) recorded at the airway opening can be used as a guide to prevent lung overdistension and hence risk of barotrauma, which, particularly in mechanically ventilated patients with acute exacerbation of COPD, may be a life-threatening complication (38,62).

The main forces opposing lung inflation are (1) PEEPi (as described in the previous section), (2) respiratory elastance, (3) flow resistance, and (4) viscoelastic forces and pendelluft (see below). A detailed analysis of all these factors has been made possible by the re-examination and re-evaluation of the interrupter technique and by its adaptation to mechanically ventilated patients (63,64,65).

## V. Flow-Interruption Technique

Originally proposed by von Neergaard and Wirz (66), the interruption technique is a simple method for measuring flow resistance that enjoyed wide popularity some decades ago. Its utilization, however, waned with the advent of the body plethysmographic method to measure airway resistance (67). In the middle and late 1980s, the interruption technique was reexamined and applied in anaesthetized animals (68–70) and humans (10,71) as well as adapted to mechanically ventilated patients (58,71). The engineering aspects of the technique as well as its physiological basis were established in a series of studies by Bates, D'An-

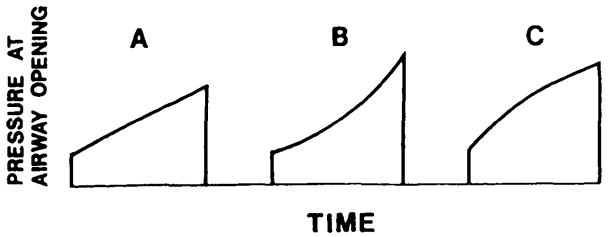


**Figure 6** Schematic diagrams illustrating time course of pressure applied at the airway opening by a constant-flow ventilator in a patient with total compliance of the respiratory system constant (A), decreasing (B), and increasing (C) during lung inflation. Case C should occur when a distinct "knee" is present on the inflation static volume-pressure curve of the respiratory system, while case B usually reflects pulmonary hyperinflation. In the presence of severe time constant inequalities within the lungs, pattern C can be present even if compliance is constant over the change in volume produced by the ventilator. (From Ref. 63.)

gelo and Milic-Emili (10–12,64,65,72). The two major variations of the interruption technique are:

1. Single breath airway occlusion during constant flow inflation
2. Multiple interruptions during the relaxed expiration

These two variations of the interruption method allow us to determine, noninvasively, the static elastance, dynamic elastance, and flow resistance of the total respiratory system (10,40,58). Furthermore, the latter can be partitioned into airway and tissue components (10,40,58). By adding an esophageal balloon-catheter system, the overall respiratory system mechanics can be partitioned into lung and chest wall components (41–43).

### A. Airway Occlusion During Constant Flow Inflation

This technique is essentially a combination of two basic approaches for measuring flow resistance that were originally described by von Neergaard and Wirz, namely, the elastic subtraction (73) and the interruption (66) methods. Although the technique may be used with any type of inflation flow waveform (constant, decelerating, and sinusoidal), most data have so far been obtained with constant flow inflation and interpreted on the basis of the viscoelastic model of the respiratory system illustrated in Figure 7. Clearly, the airway can be occluded at different lung volumes and different constant flow inflation rates. The general principles

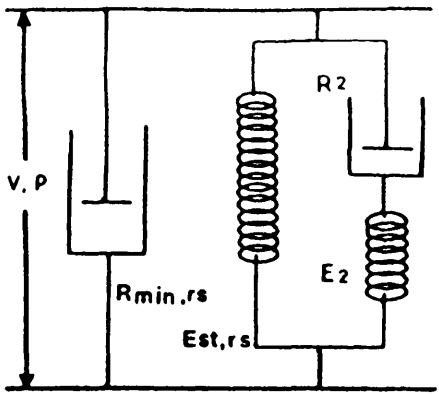


**Figure 7** Scheme of spring-and-dashpot model for interpretation of respiratory mechanics during flow interruption. Respiratory system consists of standard resistance (Rmin,rs) in parallel with standard elastance (Est,rs) and series spring-and-dashpot body (E2 and R2, respectively) that represents stress adaptation unit. Distance between two horizontal bars is analog of lung volume (V), and tension between this bars is analog of pressure at airway opening (P). (Modified from Ref. 10.)

are the same, but experimental results are significantly affected by the inflation rate as well as the lung volume at which the occlusion is performed. In general, the rapid airway occlusion during constant flow inflation is performed at the end of the mechanical lung inflation in line with the traditional techniques to measure respiratory compliance and resistance (74,75).

As illustrated in Figure 8, rapid airway occlusion during constant flow inflation is followed immediately by a sudden drop in airway pressure from its maximum value (Ppeak) to a lower value (P1) and then by a slow decay to an apparent plateau (Pplat), which is usually achieved after 3–5 seconds (10,41,43). The apparent plateau (Pplat) reflects the elastic recoil of the total respiratory system (Pst,rs) at the end-inflation lung volume or at any occluded lung volume between the start and the end of the inflation, provided there is no leak in the combined "ventilator–measuring equipment–patient's respiratory system" (e.g., a bronchial fistula or subcutaneous or mediastinal emphysema). The total difference between Ppeak and Pplat reflects the total resistive pressure drop, which includes a pure resistive element represented by the rapid pressure drop from Ppeak to P1 plus a more complex viscoelastic component, which accounts for the slow P1 − Pplat decay. The model illustrated in Figure 7 will be used to interpret the pressure behavior following airway occlusion.

### B. Theory

If the lung and the chest wall behave together as a single-compartment resistance-capacitance system, Pao after airway occlusion should immediately drop to a value corresponding to Pst,rs. This is clearly not the case (Fig. 8) in view of the gradual decay in postocclusion pressure from P1 to Pplat. The existence of P1 − Pplat indicates that, after interruption, there occurs either gas redistribution within the lung (*pendelluft*) and/or stress relaxation of the respiratory system tissues or both. Recent work (76,77) on flow interruption in anaesthetized dogs suggests that pendelluft contributes little to P1 − Pplat in normal lungs and that the respiratory tissue properties can be adequately represented by the model in Figure 7. The model consists of two compartments in parallel: a dashpot representing minimum respiratory resistance (Rmin) and a Kelvin body. The latter consists of a spring representing the static elastance of the total respiratory system (Est,rs) in parallel with a Maxwell body, i.e., a spring (E2) and a dashpot (R2) arranged serially. E2 and R2 represent viscoelastic properties of the tissues of the lung and the chest wall, whereas Est,rs and Rmin are standard elastic and resistive measurements. It must be stressed that the four-element model in Figure 7 is not intended to be a complete and perfect representation of respiratory mechanics. Rather, it is merely a useful representation of the behavior of the normal respiratory system during flow interruption. Since measurements pertain to constant flow inflation, i.e., unidirectional flow, the analysis is to some extent less complicated, because other models containing hysteresis and plastoelastic phenomena due to reversal of flow (78) may be considered not relevant to our analysis. In addition, the model in

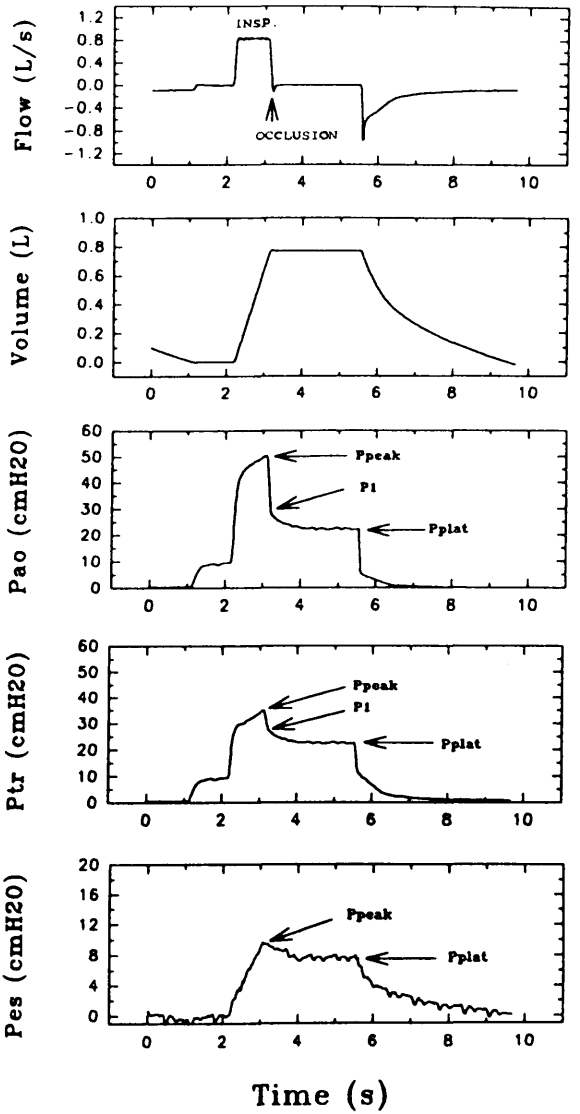


**Figure 8** Tracings (top to bottom) of flow, volume, pressure at the airway opening (Pao), pressure at the distal side of the endotracheal tube (Ptr), and esophageal pressure (Pes) in a representative patient with chronic obstructive pulmonary disease (COPD) in whom the end-inspiratory occlusion during constant flow inflation has been performed. After end-inspiratory occlusion, there was an immediate drop from its maximum value (Ppeak) to a lower value (P1) and then by a slow decay to an apparent plateau (Pplat), which is achieved after 2 seconds (see text for more explanation). In this patient no P1 was detectable on the Pes record.

Figure 7 contains no inertive elements, such as required to account for the behavior of the respiratory system when very high-frequency oscillations in pressure are applied at the mouth. This is because the only evidence of inertia that can be discerned during interruption is rapid and highly damped oscillations in Pao (or Ptr) immediately after the interruption. These oscillations vanish within 50 msec and can be allowed for backextrapolation of the subsequent pressure signal (41,64). Though simplistic, the model in Figure 7 has proven useful in interpreting the results obtained with the interrupter technique.

### C. Measurement of Elastance

#### *Static Elastance*

The end-inspiratory airway occlusion maneuver has been widely used to compute the static elastance of the total respiratory system (Est,rs) or its reciprocal, the static compliance (Cst,rs), according to the traditional formula (still used with most modern, microprocessor-equipped ventilators):

$$\text{Est,rs} = \frac{\text{Pplat} - \text{PEEP}}{\text{VT}} \tag{4}$$

where Pplat is the end-inspiratory Pst,rs and PEEP (or ZEEP in absence of PEEP set by the ventilator) is the end-expiratory pressure with unoccluded airway. This formula is valid provided that the preceding expiration was complete, i.e., that flow was nil at the end of expiration, and hence the mechanical lung inflation started from Vr. This is never the case in mechanically ventilated patients with acute exacerbation of COPD because of dynamic pulmonary hyperinflation and intrinsic PEEP (18,24). Accordingly the correct formula to compute Est,rs is:

$$\text{Est,rs} = \frac{\text{Pplat} - \text{PEEP} - \text{PEEPi}}{\text{VT}} \tag{5}$$

where PEEPi represents the end-expiratory pressure during the brief end-expiratory airway occlusion, and VT represents the change in volume from EELV (22,53). In mechanically ventilated COPD patients, the true static elastance can be overestimated up to 100% if PEEPi is not taken into account (24). Because of the interdependence of several factors, including patient's respiratory mechanics and the ventilator settings, PEEPi, and hence the magnitude of the error in the computation of elastance is difficult to predict.

Using the esophageal balloon technique, Est,rs can be partitioned into lung and chest wall components. This has been done in normal anesthetized subjects (11) and in mechanically ventilated COPD patients as shown in Table 2. The values of static elastances in mechanically ventilated COPD patients are similar to those of normals, except for slightly higher values of Est,w found by Ranieri et al.

**Table 2** Values of Elastance (in $cmH_2O/L$) in Normal Anesthetized Subjects and COPD Patients During CMV with Common Ventilatory Settings

| Patients | Respiratory system | Lung | Chest wall | Ref. |
|---|---|---|---|---|
| Normals | 14.5 ± 2.1 | 8.2 ± 0.4 | 6.3 ± 0.3 | (11) |
| COPD | 15.3 ± 4.0 | 7.9 ± 2.1 | 7.4 ± 2.4 | (41) |
| COPD | 17.4 ± 1.8 | 6.7 ± 1.0 | 10.7 ± 1.4 | (42) |
| COPD | 12.9 ± 0.5 | 7.7 ± 0.8 | 5.2 ± 6.3 | (43) |

(42), which were probably a result of the greater dynamic hyperinflation in those patients.

Measurement of elastance by means of end-inspiratory occlusion [Eq. (5)] assumes that the volume-pressure (V-P) relationship is linear over the inflation volume range. This can be assessed by performing multiple interruptions during the relaxed expiration following release of airway occlusion (18,23). After the apparent plateau in airway pressure has been observed (3–5 sec), the airway occlusion is released and a series of brief interruptions is performed at the airway opening, for example, using a shutter. At each interruption, flow becomes zero, volume remains unchanged, and airway pressure rises to an apparent plateau, reflecting Pst,rs at any interrupted volume. However, the duration of the brief interruptions throughout expiration may not be long enough to display the plateau in Pao, particularly in patients with $\tau$ inhomogeneity. Hence the value of Pao during the occlusions might not represent the true Pst,rs at any lung volume above FRC. This is clearly a limitation in the use of this technique in mechanically ventilated patients. Nevertheless, useful results have been obtained in the clinical settings (18,23). By plotting the plateau in airway pressure against the corresponding volume above and below the tidal end-expiratory lung volume, the expiratory V-P relationship can be obtained, as shown in Figure 4. Gottfried et al. (23) and Broseghini et al. (18) observed that most of the interrupter points could fit a linear regression analysis and computed the total respiratory system static compliance (Cst,rs, the reciprocal of Est,rs) from the slope of the regression line (Fig. 4). A linear V-P relationship throughout most of the relaxed expiration was observed in the majority of patients (18,23). In some patients the V-P relationship may exhibit a continuous curvilinearity, which does not allow computation of Est,rs by linear regression analysis (23). As shown in Figure 4, the technique of multiple interruptions provides not only the value of Cst,rs (and its reciprocal Est,rs), but also the magnitude of dynamic pulmonary hyperinflation and the amount of intrinsic PEEP. Values of Cst,rs computed by means of the multiple interruption technique throughout the relaxed expiration may be slightly higher than Cst,rs computed from the end-inspiratory occlusion, because of some curvilinearity toward the end of the lung inflation probably due to pulmonary hyperinflation (23).

*Dynamic Elastance*

The dynamic elastance of the total respiratory system (Edyn,rs) is obtained by dividing the difference in Pao at points of zero flow by the inflation volume (10). In COPD patients the end-expiratory pressure at zero flow corresponds to PEEPi,dyn or to PEEP + PEEPi,dyn. Because of dynamic pulmonary hyperinflation, this lags behind the onset of the positive pressure swing. At the end of the mechanical lung inflation, the point where inspiratory flow becomes zero corresponds to P1, as illustrated in Figure 8. Therefore, the correct formula to compute dynamic elastance is the following:

$$\text{Edyn,rs} = \frac{\text{P1} - \text{PEEP} - \text{PEEPi,dyn}}{\text{VT}} \tag{6}$$

The difference between dynamic and static elastance of the total respiratory system (Edyn,rs > Est,rs) is determined not only by the fact that P1 > Pplat, but also by the difference between dynamic and static PEEPi (PEEPi > PEEPi,dyn). In normal lungs, stress adaptation phenomena play a major role in determining P1 − Pplat, and there is no PEEPi (10). In contrast, PEEPi is a common finding in COPD patients. The difference between PEEPi and PEEPi,dyn, as well as P1 − Pplat, includes a major component due to time constant inhomogeneity (pendelluft).

### D. Measurement of Resistance

Conventionally, the value of total flow resistance in mechanically ventilated patients is obtained by dividing the total drop in pressure from Ppeak to Pplat by the immediately preceding flow, according to the formula (75,79):

$$R_T = \frac{\text{Ppeak} - \text{Pplat}}{\dot{V}I} \tag{7}$$

where $\dot{V}I$ is the flow immediately preceding the airway occlusion. However, as previously mentioned and illustrated in Figure 8, the total drop from Ppeak − Pplat, in Pao and Ptr, is made by the rapid Ppeak to P1 fall and by the slow P1 to Pplat decay. Hence, $R_T$, obtained as described in Eq. (7), includes at least two "resistances," one related to the Ppeak − P1 drop and an other related to the P1 to Pplat decay, which is due to the discharge of the spring E2 into the dashpot R2.

The "rapid component" of total flow resistance can be calculated using the formula:

$$\text{Rint} = \frac{\text{Ppeak} - \text{P1}}{\dot{V}I} \tag{8}$$

where Rint is the "interrupter" resistance, reflecting the dashpot R1. In the first instance (58,60), $R_T$ and Rint were termed maximum and minimum respiratory

resistance (Rmax,rs and Rmin,rs), respectively, and interpreted according to the frequency-dependence analysis of the behavior of the respiratory system (60). If RT and Rint are measured from Pao rather than Ptr, they include the flow resistance due to the endotracheal tube and equipment. After subtraction of the flow resistive component due to endotracheal and ventilator tubings (either in vitro or in vivo by measuring Ptr directly) Rmin,rs was interpreted as the minimum respiratory resistance at very high frequency, i.e., approaching $\infty$, whereas Rmax,rs was assumed to represent maximum respiratory resistance at very low frequency, i.e., approaching 0. Therefore, in line with the analysis of frequency-dependence of resistance (79–81), it was stressed that the (Rmax,rs − Rmin,rs) difference could reflect, to some extent, the amount of frequency dependence of resistance. In fact, the Rmax,rs − Rmin,rs difference was found to be larger in mechanically ventilated COPD patients, who are known to have frequency dependence of resistance due to $\tau$ inhomogeneity, compared to mechanically ventilated patients without chronic airway disease (18,24,58). Recently, Bates and Milic-Emili (64) and D'Angelo et al. (10–12) have clarified both in theory and experimentally the physiological significance of Rint and RT.

### *Endotracheal Tubes and Equipment Resistance*

Measurements obtained in vitro using air, oxygen-enriched air, and anaesthetic gases have shown that the pressure-flow relationship of all the endotracheal tubes plus measuring equipment (e.g., Fleisch pneumotachograph) is markedly curvilinear and fits the classic Rohrer's equation

$$\text{Pres} = K_1\dot{V} + K_2\dot{V}^2 \tag{9}$$

where Pres is the resistive pressure, and $K_1$ and $K_2$ are constants, and the following power function:

$$\text{Pres} = a\dot{V}^b \tag{10}$$

Values of a and b for the five endotracheal tubes are reported in Figure 9, whereas values of $K_1$ and $K_2$ are shown in Table 3.

Equations (9) and (10) have been used to subtract the flow resistance of ET tubes from Rint and RT obtained from measurement of Pao at the proximal end of the tube (18,58). However, the Ett plus measuring equipment flow resistance can also be subtracted in vivo when pressure is measured at the distal tip of the Ett by means of a polyethylene catheter with side holes (Ptr, tracheal pressure). However, measurement of Ptr may present problems. First, mucus may accumulate in the Ett as well as in the trachea, affecting the transmission of pressure to the pressure transducer. Second, there may be underestimation of Ptr due to the Bernoulli's effect (83). This is more important in pediatric studies because of the smaller diameter of the Etts. Third, due to the abrupt change in diameter between the

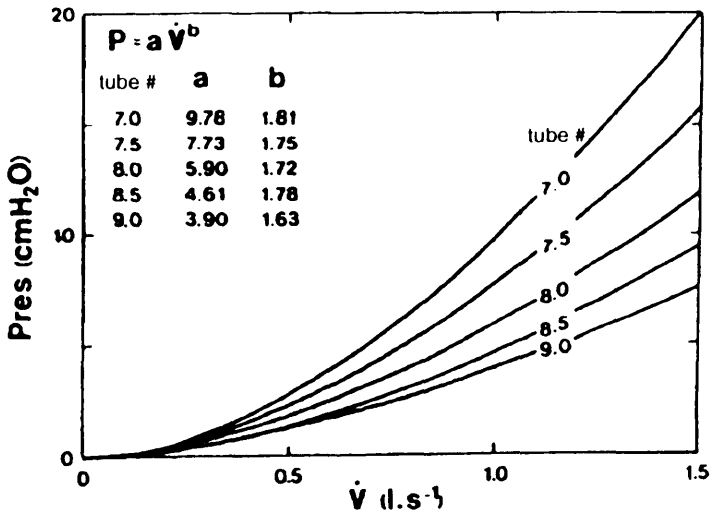


**Figure 9** The relationship between resistive pressure (Pres) and air flow ($\dot{V}$) for endotracheal tubes (and connectors) of representative sizes is shown. Also indicated are the results obtained by fitting measurements to a power function of the form Pres = $a\dot{V}^b$, where a and b are constants. (Modified from Ref. 23.)

Ett and the human trachea, the flow in the boundary layer tends to reverse. As a result the flow through the expansion is frequently turbulent (84). This effect can be attenuated by placing the catheter about 2 cm beyond the tip of the Ett. However, since the distal tip of the Ett may be close to the tracheal carina, care must be taken such that the tip of the catheter does not extend into the main right bronchus. To prevent the interference of secretions, the catheter should be flushed frequently (41,85). Ett resistance measured in vivo has been found to be greater

**Table 3** Resistive Properties of Endotracheal Tubes

| Internal diameter of endotracheal tube (mm) | $K_1$ ($cmH_2O\ L^{-1}\ sec$) | $K_2$ ($cmH_2O\ L^{-2}\ sec^{-2}$) |
|---|---|---|
| 7.0 | 0.69 | 10.3 |
| 7.5 | 0.13 | 8.1 |
| 8.0 | 0.13 | 6.5 |
| 8.5 | 0.12 | 4.6 |
| 9.0 | 0.33 | 3.4 |

*Source*: Ref. 82a.

than that in vitro because of secretions and also accretions (solid stuff) in the Ett lumen and kinking of the Ett in the upper airway, particularly when inserted through the nose (41,86).

### *Interrupter Resistance*

Neergaard and Wirz (66) suggested that Rint essentially reflects airway resistance (Raw). In experiments on open-chest dogs in which changes in alveolar pressure were measured with the capsule technique (76), it was found that the immediate changes in transpulmonary pressure (P1) following rapid airway occlusion during relaxed expiration were virtually identical to the preinterrupted pressure drop between the trachea and alveoli (76), indicating that Rint,L does not include a component due to lung tissue. In anesthetized paralyzed humans (11) and in mechanically ventilated COPD patients (41,43), there was no appreciable change in esophageal pressure (Pes) following airway occlusion. Moreover, the Pes records included substantial esophageal artefacts, and the occlusion valve was rather slow (closing time: 40–120 msec). Using a faster valve (closing time: 10–15 msex) and ensemble averaging of 30–40 breaths, Prandi et al. (87) recently found that humans also exhibit a definite, though small, Rint,w amounting to $0.47 \pm 0.17$ (SD) $cmH_2O/L/sec$. A similar, low value of Rint,w was also found by Polese et al. (41) in mechanically ventilated patients when RintI was subtracted from Rint,rs. Therefore, in humans, Rint includes a small chest wall component as well Raw, as originally proposed by Mead and Whittenberger (88). This is also true in dogs and cats (69,77). However, in mechanically ventilated COPD patients, in whom Raw is markedly increased, Rint,rs is essentially identical to Raw because the contribution of the chest wall becomes insignificant (41,43), and hence the interruption technique [Eq. (8)] allows determination of patients' airway resistance.

An important technical aspect of the interruption technique to measure Raw is the occlusion time of the valve. Ideally, the valve should close instantaneously. In practice, there is a finite period of time during which any valve proceeds between its open and close configuration. During that period, gas continues to flow through the valves, thereby affecting the measurement of pressure signal. Kochi et al. (70) suggested a formula to correct measurement of interruption resistance for gas flow into the lungs during the occlusion time of the valve with common ventilators (Servo 900C). Bates and Milic-Emili (64) have shown that Ppeak − P1 may be underestimated by approximately 7% in normal lungs with a closing time of the valve of 12 msec. Clearly a rapid occlusion valve is required to obtain correct measurements. For most applications a valve closing in 10 msec or less is sufficient to accurately measure interruption resistance (64), though clinically useful results would be obtained also with a valve closing in 15–20 msec (64). In this connection it should be noted that studies in mechanically ventilated patients

by means of the interruption methods are technically easier than in nonintubated subjects (68) because a rigid endotracheal tube bypasses the compliant region of the upper airway. A detailed methodological discussion of the interrupter method can be found in a recent review by Bates and Milic-Emili (64).

The interruption resistance during expiration has been measured by Gottfried and colleagues in cats (69), anesthetized humans (71), and mechanically ventilated patients (23). During the relaxed expiration Pst,rs = Pres, though with the limitations mentioned previously about viscoelastic pressures, which may prevent a complete plateau reflecting true Pst,rs with brief occlusions. Nevertheless, the apparent plateaus in airway pressure that have been used to drawn the expiratory V-P curve (Fig. 4) can be used also to describe the pressure flow relationship throughout the relaxed expiration by plotting the apparent plateau against the flow immediately preceding the interruption. Gottfried et al. (23) have found that in all mechanically ventilated patients the pressure-flow relationship was nonlinear but could be fitted to the power function reported in Eq. (10). Representative results of pressure-flow relationships are shown in Figure 10. It is noteworthy that the downward concavity of the pressure-flow relationship obtained by means of the interruption technique in mechanically ventilated COPD

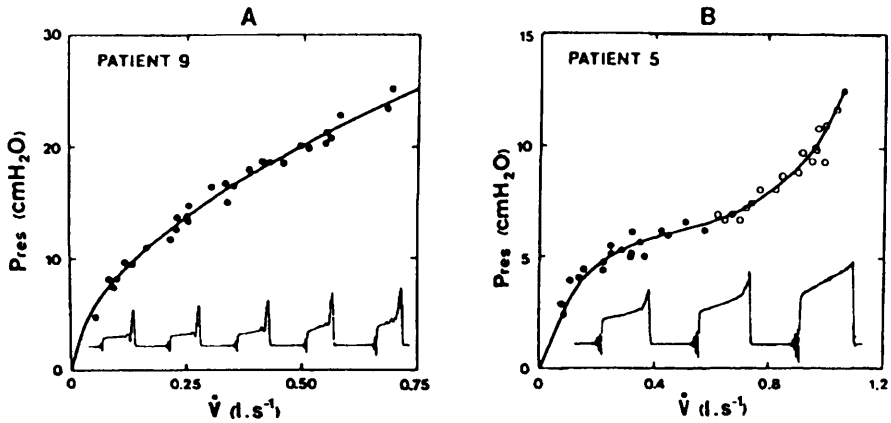


**Figure 10** Relationship between resistive pressure (Pres) and expiratory flow ($\dot{V}$) in two patients. (A) Pres-$\dot{V}$ relationship is concave to the flow axys associated with expiratory flow limitation (closed circles) throughout expiration. This is indicated (insert) by the presence of characteristic "supramaximal" flow transients after each period of flow interruption. (B) Pres-$\dot{V}$ relationship is concave upward early in expiration with the development of dynamic airway compression and flow limitation (closed circle). This is indicated by the presence of "supramaximal" flow transients only later in expiration, coincident with the upward convexity in Pres-$\dot{V}$ relationship. (From Ref. 23.)

patients was always associated with "spikes" in the postinterruption flows, further supporting the notion that expiratory flow limitation is common in mechanically ventilated patients with acute exacerbation of COPD (23,43).

### *Additional Resistance*

As shown in Figure 8, after the rapid fall from Ppeak to P1 there is a further slow decrease in Ptr (or Pao) from P1 to Pplat. The additional resistance ΔRrs may be computed according to the formula:

$$\Delta Rs = \frac{P1 - Pplat}{\dot{V}I} \tag{11}$$

Since the slow decay from P1 to Pplat is not in phase with flow, as it occurs after flow has stopped, the P1 − Plat difference does not reflect a pure (Newtonian) resistive behavior. Indeed, it reflects two phenomena: (1) transfer of a small volume of gas from alveoli with high pressure to units with low pressure (i.e. pendelluft), which may be brought about by time constant inequality within the lungs, and (2) stress adaptation phenomena of the respiratory (lung and chest wall) tissues. In the normal lung, ΔRrs is mainly due to viscoelasticity (76), whereas in disease, and particularly in patients with acute exacerbation of COPD, time constant inequality probably contributes significanlty to ΔRrs.

The nature of ΔRrs may be interpreted as follows. When the model in Figure 7 is elongated at constant speed (v), the charge of the spring E2 increases with the inspiratory time (TI). If a flow interruption maneuver is performed by sudden halting the relative movement of the two horizontal bars in Figure 7, the length of the spring E2 will decay exponentially to its equilibrium length. In terms of the model, the postinterruption P1 − Pplat decay may be interpreted as the spring E2, resulting in resistive energy dissipation in the dashpot R2. The amount of relaxation of tension (*stress relaxation*) thus depend from the degree of stretch of spring E2 at time of interruption of flow. Since ΔRrs is not a pure (Newtonian) resistance, the term effective resistance (or impedance) seems preferable to define ΔRrs. It has been shown in both anesthetized humans (11) and mechanically ventilated COPD patients (41,42) that ΔRrs basically reflects ΔRL, with little contribution from ΔRw, virtually entirely reflecting viscoelastic behavior of the chest wall tissues.

### *Total Respiratory System Resistance*

Since total respiratory system resistance (Rrs) is given by Rint, rs + ΔRrs, it follows that $R_T$ computed from Eq. (7) represents Rrs. This equation can be actually viewed as an application of the elastic subtraction principle of von Neergaard and Wirz (73). Indeed, Eq. (7) reflects the application of the interruption method (66), as pointed out by Liistro et al. (68), to spontaneously breathing

normal humans. Rrs is higher in COPD than in normal anesthetized subjects (10), largely because of a marked increase in Raw but in part also because of the increased ΔRrs, which, in COPD patients with ARF, is likely to reflect a large amount of τ inhomogeneity within the lungs (58,81). In COPD patients with ARF the chest wall contribution to ΔRrs is similar to that in normal subjects (41,43).

Measurements of respiratory resistance by means of the airway occlusion technique during constant flow inflation are not only a useful approach to assess changes in resistance for clinical purposes, but also provide a powerful tool for studying the mechanical properties of the lung and the chest wall under different physiological conditions.

### *Effects of Flow and Volume on Resistance*

The traditional concepts about the flow- and volume-related changes in flow resistance assumed that resistance should increase with increasing flow and decrease with increasing lung volume. The latter effect is the consequence of the direct relationship between bronchial caliber and lung volume (89), whereas the former is well described by Rohrer's equation [Eq. (8)].

Application of the airway occlusion during constant flow inflation in normal anesthetized humans (10) and in mechanically ventilated COPD patients (40,43) has shown that Raw increases with increasing flow and decreases with increasing volume. In contrast, Rrs decreases with increasing flow and increases with increasing lung volume (40), contrary to traditional notion. A similar behavior to that of Rrs was also found for total pulmonary resistance (RL) in both anesthetized normals (11) and mechanically ventilated COPD patients (43). The contribution of chest wall resistance (Rw) to Rrs in mechanically ventilated COPD patients is small in comparison to normals, probably because of the increased Raw and ΔRL (43). The different behavior of Rrs and RL compared to Raw is explained by the behavior of ΔRrs and ΔRL. ΔRw was found to account only for 10% of ΔRrs (41,43). ΔRrs increases with increasing volume and decreases with increasing flow, as predicted by the model in Figure 7, whereas Raw increases with increasing flow [Eq. (6)] and decreasing volume, the final behavior of Rrs will depend upon the balance between the two. With higher flow rate, e.g., >1 L/sec, the increase in Raw becomes more important such that Rrs increases with increasing flow at fixed inflation volume (Fig. 11).

In addition to their physiological interest, the results by Kochi et al. (70), D'Angelo et al. (10), Tantucci et al. (40), and Guerin et al. (43) have important implications in the clinical setting. First, measurement of resistance is clearly influenced by the ventilator settings such that differences between patients as well as differences in time in the same patients might well be due to either intentional or inadvertent changes in the ventilator settings rather than to changes in patients' respiratory mechanics because of treatment or complications. Therefore, compari-

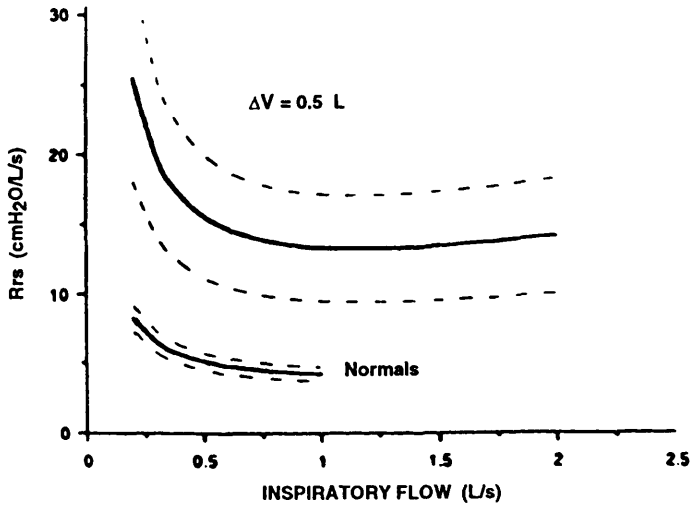


**Figure 11** Average (± SE) relationship between total resistance of respiratory system (Rrs) and inspiratory flow inflation volume ($\Delta V$) of 0.5 L in 6 sedated paralyzed COPD patients with ARF and 16 normal anesthetized paralyzed subjects. (From Ref. 40.)

son of values of resistances are meaningless unless V and $\dot{V}$ are standardized. In this connection it is noteworthy that the interruption technique during constant flow inflation also allows standardization for the preceding volume history. Second, at low flow rates, which are the flow rates during spontaneous breathing, the respiratory tissue resistance and pendelluft are the major components of the resistive load to breathing, even more than pure airway resistance (90).

## VI. Work of Breathing

During CMV, all the pressure needed to inflate the respiratory system and to sustain alveolar ventilation is provided by the ventilator. Accordingly, there would seem no need to compute the work of breathing under conditions that do not imply energy expenditure from the patient's respiratory muscles. Furthermore, the large volume and low frequency settings of mechanical ventilator differ from the rapid shallow breathing pattern exhibited by COPD patients with ARF. However, it is possible to mimic the spontaneous breathing pattern by adjusting the ventilator setting. In addition, measurement of "passive" work represents a unique possibility to measure the total work done on the respiratory system, i.e., including the chest wall. The work done by the thorax during spontaneous breathing may be higher than during passive mechanical inflation in view of the stiffer thorax when

the inspiratory muscles contract (91) as well as the possible presence of paradox movements of the abdomen (inward motion during inspiration) and hence a larger chest wall distortion.

The increase in the work of breathing in mechanically ventilated patients with acute exacerbation of COPD, compared to normal anesthetized subjects, is due mainly to PEEPi, although Raw and $\Delta$Rrs contribute to it as well (90). The contribution of the chest wall mechanics to the increased workload is negligible (41,90). A significant portion of the work done by the ventilator is required to overcome the resistance offered by the Ett. Since the latter is flow dependent, it will increase with higher flow rate and smaller internal diameter of the ET tube. Measurement of "passive" work of breathing, while mimicking the spontaneous "rapid shallow breathing," shows that intrinsic PEEP is probably the most important burden in patients with acute exacerbation of COPD, such that the use of external PEEP to counterbalance PEEPi during assisted ventilation and weaning seems warranted (8,92).

## VII. Relaxed Expiration

During CMV with a ventilator setting well adapted to the patient, the driving pressure for expiration is provided by the elastic recoil stored in the total respiratory system during the preceding lung inflation. The opposing force is the total expiratory flow resistance.

In anesthetized cats (93), the time decay of the expired volume may be described by a monoexponential function:

$$V(t) = VO \cdot e^{-t/\tau_{rs}} \tag{12}$$

where V is the exhaled volume at any time (t) during the relaxed expiration, VO is the total exhaled volume, and $\tau_{rs}$ is the respiratory system time constant. In intubated humans (94), the expiratory flow-volume curve exhibits a concavity toward the volume axis because of the nonlinear resistive properties of the lungs (11,43) and Etts (94). In this case Eq. (12) is not valid. Other factors may also affect the shape of the volume-flow curve during passive expiration. Indeed, COPD patients with acute exacerbation always exhibit expiratory flow limitation, which makes the decay in volume during the relaxed expiration a complex process that cannot be readily described by a single equation. As can be seen in Figure 3, the presence of expiratory flow limitation changes completely the shape of the expiratory volume-flow curve, determining a convexity rather than a concavity toward the volume axis. In addition, $\tau$ inhomogeneity within the lungs, which is not present in normal lungs, and viscolelastic behavior (Fig. 7) implies a slow component during lung deflation. Recently, Chelucci et al. (95) reported that in ARDS patients as well as in normal mechanically ventilated subjects, the volume

decay during passive expiration can be well described by a biexponential function (95,95a). To our knowledge, however, that analysis has not been applied yet to flow-limited COPD patients with ARF.

Since the model illustrated in Figure 7 has important implications for volume decay during passive expiration, it is also important for determining the magnitude of dynamic increase in FRC. Since the elastic recoil is the pressure driving expiration, any "short" end-inspiratory hold will decrease it because of dissipation of the energy stored in the spring E2 into the dashpot R2. By contrast, without any end-inspiratory hold, the energy stored in E2 is available to drive expiratory flow (43). According to this analysis, abolition of the end-inspiratory pause, together with low frequencies and low TI/TT (high inspiratory flow rate), can be used to decrease dynamic pulmonary hyperinflation (and PEEPi) (43).

## VIII. Clinical Implications

The major clinical implications resulting from the interrelationship between patients' respiratory mechanics and CMV concern the cardiorespiratory effects of PEEP, risk of pulmonary barotrauma, and "controlled mechanical hypoventilation" (permissive hypercapnia).

### A. Ventilator Settings

A large series of measurements of respiratory mechanics in mechanically ventilated COPD patients with ARF have shown that pulmonary hyperinflation is the hallmark. Some of the causes and consequences of pulmonary hyperinflation are listed in Table 4.

Endotracheal tubes with large internal diameter (i.d.) as well as large and short ventilator tubings should be used to *reduce the added resistance*. The resistance of the expiratory valve should also be taken into account, which might be important. Frequent *suctioning of secretions* from natural and artificial (the tube) airways should also decrease flow resistance. In the setting of the ventilatory parameters the *longest expiratory time* compatible with the targeted arterial blood and patients' comfort should be used. A long expiratory time can be obtained by using high inspiratory flow rates, other factors remaining unchanged. The increase in peak cycling pressure with high inspiratory flows is due to a rise in pressure dissipation in the endotracheal tube and, in general, does not herald an enhanced risk of barotrauma. End-inspiratory alveolar pressure can be measured by means of end-inspiratory occlusion, as illustrated in Figure 8. It has been shown that bronchodilators improve the rate of lung emptying through their relaxant effect on bronchial smooth muscles (44,96); methylxanthines and adrenergic agonists can act synergically and result in marked reductions of pulmonary hyperinflation and intrinsic PEEP, though their effect seems to be short-lived (44,96).

**Table 4** Pulmonary Hyperinflation

| |
|---|
| Causes |
| Loss of lung recoil |
| Airway closure |
| Increased flow resistance |
| Expiratory flow limitation |
| Short expiratory duration |
| Large $V_T$ (or $\dot{V}_E$) |
| Consequences |
| Increased inspiratory workload |
| Elastic + threshold (PEEPi) |
| Decreased inspiratory muscle pressure-generating capacity |
| Length-tension characteristics |
| Geometric considerations |
| Risk of barotrauma |

### B. Barotrauma

Pulmonary barotrauma, which is defined by the presence of extraalveolar air in locations where it is not normally found, is a well-recognized and feared event in mechanically ventilated patients (97). It occurs in 10–20% of all patients receiving mechanical ventilation (2). Among all forms of ventilator-induced barotrauma, tension pneumothorax is not uncommon and may be a life-threatening condition that requires rapid identification and prompt treatment. Ventilator-induced barotrauma develops after rupture of an overdistended alveolus. Mechanical ventilation by itself cannot be considered the only cause of barotrauma. Rather, mechanical ventilation can be an aggravating factor. Risk factors for ventilator-associated barotrauma producing alveolar overdistention include the use of volume ventilators, high tidal volumes, high inflation and inspiratory airway pressure, and excessive levels of PEEP (97). Pulmonary barotrauma can occur in patients with preexisting alveolar distension, such as patients with acute exacerbation of COPD and status asthmaticus. In those patients, the use of large tidal volume may displace ventilation toward the upper flat portion of the lung volume-pressure relationship (1), determining alveolar overdistension. In addition, the larger the inflation volume, the longer the time needed for expiration such that large tidal volumes can enhance pulmonary hyperinflation. The use of the smaller than conventional tidal volumes, e.g., 6–7 rather than 10–12 ml/kg, allows ventilation of the lungs of patients with acute exacerbation of COPD and status asthmaticus in the linear portion of the volume-pressure relationship (18). Apparently, the incidence of all forms of pulmonary barotrauma is higher in patients with asthma than in patients with acute exacerbation of COPD. Whether

this is related to a greater degree of pulmonary hyperinflation remains to be established.

The clinical importance of low tidal volumes has been noted by Darioli and Perret (98). Survival rate of mechanically ventilated patients with status asthmaticus was increased using the so-called controlled mechanical hypoventilation, which is characterized by lower than usual tidal volume and permissive hypercapnia. When using this approach, arterial pH rather than $Paco_2$ needs to be monitored. Whether the pH when <7.2 should be controlled by administration of bicarbonates remains controversial. Recently, Tuxen et al. (30) proposed measuring the total expired volume (VEI) as a reliable indicator of the severity of pulmonary hyperinflation in mechanically ventilated asthmatics. VEI was measured allowing a complete passive expiration from the end-expiratory inflation volume to the equilibrium volume of the total respiratory system as in the example shown in Figure 4. Tuxen et al. (30) suggested keeping VEI less than 20 ml/kg to prevent excessive pulmonary hyperinflation and the related increased risk of barotrauma. Standard measures to limit alveolar overdistension include decrease in end-inflation alveolar pressure, tidal volume, PEEP, and intrinsic PEEP. In COPD patients on CMV, Rossi et al. (99) have shown that the use of small tidal volume (5–6 ml/kg) was associated with worse arterial blood gases than with conventional tidal volumes, because of greater ventilation-perfusion mismatching. However, cardiac output and peripheral oxygen delivery were much better with controlled mechanical hypoventilation than with the conventional settings. Although precise guidelines are not available, targets of mechanical ventilation are under current reexamination and revision to limit as much as possible the lung damage caused by mechanical ventilation (2,38).

### C. Application of PEEP

Traditionally, application of PEEP in mechanically ventilated patients with acute exacerbation of COPD has been discouraged in order to avoid excessive hyperinflation and enhanced risk of barotrauma. In recent years, however, it has become apparent that application of judicious low levels of PEEP can be of benefit in COPD patients during assisted mechanical ventilation and weaning in order to reduce the patients' inspiratory muscle effort (8). It should be stressed, however, that while the application of PEEP may reduce PEEPi and hence unload the inspiratory muscles, it does not decrease pulmonary hyperinflation. Accordingly, its use during CMV with relaxed respiratory muscles seems unwarranted. Nevertheless, clinical studies in which PEEP was applied to COPD patients on CMV have been useful for a better comprehension of the interaction between PEEP and PEEPi (32,42,92,99–101). These studies have shown that "low" levels of PEEP are safe, i.e., they do not produce either an increase in pulmonary hyperinflation or a decrease in cardiac output. In line with the waterfall theory of flow limitation,

it has been observed that PEEP does not affect respiratory mechanics (elastance and resistance), lung volume, and cardiac function until a "critical" level, somewhat lower than initial PEEPi, is exceeded (92). There is still controversy concerning the level of the "safe" PEEP. Some authors claim that the level of PEEP that generates adverse mechanical and cardiovascular effects is unpredictable and should be assessed on an individual patient basis (32,100). Ranieri and colleagues (42) found that neither FRC nor cardiac output changed until the applied PEEP exceeded 85% of the initial PEEPi, on average. Different results were obtained by Tuxen (102), who discouraged application of PEEP in mechanically ventilated patients with airflow obstruction because of the risk of pulmonary hyperinflation. Although this discrepancy has not been fully clarified, it appears that the patients studied by Tuxen (102) had mostly status asthmaticus rather than exacerbation of COPD. Whether mechanically ventilated asthmatics have expiratory flow limitation remains to be established. Measurement of PEEPi and assessment of expiratory flow limitation should precede application of any level of PEEP in mechanically ventilated patients with exacerbation of asthma and/or COPD.

## IX. Conclusions

CMV is frequently used in patients with acute exacerbation of COPD in order to control the alveolar ventilation and the arterial blood gases as well as rest the respiratory muscles. During this period detailed measurements of patients' respiratory system mechanics can be easily obtained. The flow-interruption technique has been proved to be a powerful tool to measure patients' elastance and resistance during constant flow inflation and relaxed expiration. Particularly important is the measurement of intrinsic PEEP because of its many implications, not only during CMV, but also during assisted ventilation and weaning. Such measurements can be easily performed at the bedside, noninvasively, and are suitable for monitoring through microprocessor facilities.

Measurement of respiratory mechanics during CMV not only allows assessment of status and progress of the underlying pathology as well as of the effects of treatment (e.g., bronchodilators), but may also help to prevent excessive pulmonary hyperinflation and enhanced risk of pulmonary barotrauma. Whether controlled hypoventilation and permissive hypercapnia may be extensively applied to COPD patients with acute exacerbation remains to be established.

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# 29

# Ventilatory Management in Severe Airflow Obstruction

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## I. Pathophysiology of Airflow Obstruction

Complex physiology complicates the acute management of patients with severe airflow obstruction and renders them problematic during withdrawal from ventilatory support. As detailed elsewhere in this volume, hypoxemia, pulmonary hypertension, and heart failure clearly predominate as management problems in some cases and contribute to acute exacerbations in most others. The primary difficulty leading to ventilator dependence, however, is most often a simple disparity between ventilatory capability and demand.

The ventilatory pump must repeatedly expand the chest against resistive and elastic impedance. A simplified equation of motion for the ventilatory system describes the total inspiratory pressure requirement ($PI_{tot}$) as the sum of flow resistive ($P_{res}$) and elastic ($P_{el}$) pressure components:

$$PI_{tot} = P_{res} + P_{el}$$

The total elastic pressure is comprised of the incremental pressure needed to inflate the respiratory system by the tidal volume ($P_{elt}$) and any residual elastic pressure ($P_{ex}$) remaining at end-exhalation that must be overcome before gas begins to flow into the lungs. Therefore, this equation can be rewritten:

$$P_{I_{tot}} = P_{res} + P_{elt} + P_{ex}$$

The individual components of this equation can be expressed in terms of the variables that influence them. Ignoring the contributions of inertance and viscoelastance, $P_{res}$ is determined by mean inspiratory resistance ($R_i$) and average inspiratory flow rate [$\dot{V}E/(t_i/t_{tot})$], $P_{elt}$ by tidal volume ($\dot{V}E/f$) and compliance (C), and $P_{ex}$ by pressures that are intentionally applied (PEEP) and those that are spontaneously generated in the process of dynamic hyperinflation (auto-PEEP, AP (Fig. 1)):

$$P_{I_{tot}} = [\dot{V}E/(t_i/t_{tot})]\ R_i + \dot{V}E/(fC) + (PEEP + AP)$$

The flow resistive, tidal elastic, and residual elastic components are all elevated in the setting of a COPD exacerbation. The flow resistive element is increased by airway secretions, bronchospasm, and mucosal edema, as well as by a reduced number of functional conducting pathways. Once the bronchi are significantly narrowed, further reductions in airway caliber cause the pressure required to drive airflow to increase markedly. The nature of the flow resistance undoubtedly varies with the specific disease process, even if maximal expiratory flow rates are similar. For example, the severity of flow resistance can be markedly different in inspiration and expiration if tissue recoil pressure is diminished (e.g., by emphysema). Here the problem is not so much with the innate caliber of the native airway, but rather with its tendency to collapse. Expiratory resistance is accentuated by vigorous breathing efforts and by increases of minute ventilation. As the equation of motion indicates, a reduction in the inspiratory time fraction (without modification of the $\dot{V}E$ requirement) will increase the inspiratory flow resistive pressure loss during inspiration (but may also reduce the gas trapping and elastic pressure losses associated with auto-PEEP).

### Dynamic Hyperinflation

#### *Definitions*

Dynamic hyperinflation occurs whenever insufficient exhalation time prevents the respiratory system from returning to its resting end-expiratory equilibrium volume between adjacent tidal cycles (1). Auto-Peep ("intrinsic" PEEP) is defined as the positive difference between end-expiratory alveolar pressure and the end-expiratory airway pressure selected by the clinician (PEEP or CPAP). This positive pressure difference drives flow throughout exhalation until deflation is actively interrupted by the subsequent inspiratory cycle. Auto-PEEP is therefore the residual flow–driving expiratory pressure that remains just prior to the initiation of inspiratory effort. It should be noted that dynamic hyperinflation and auto-PEEP are not necessarily linked. When hyperinflation occurs gradually, there may be sufficient remodeling of thoracic and pulmonary structures to attenuate or

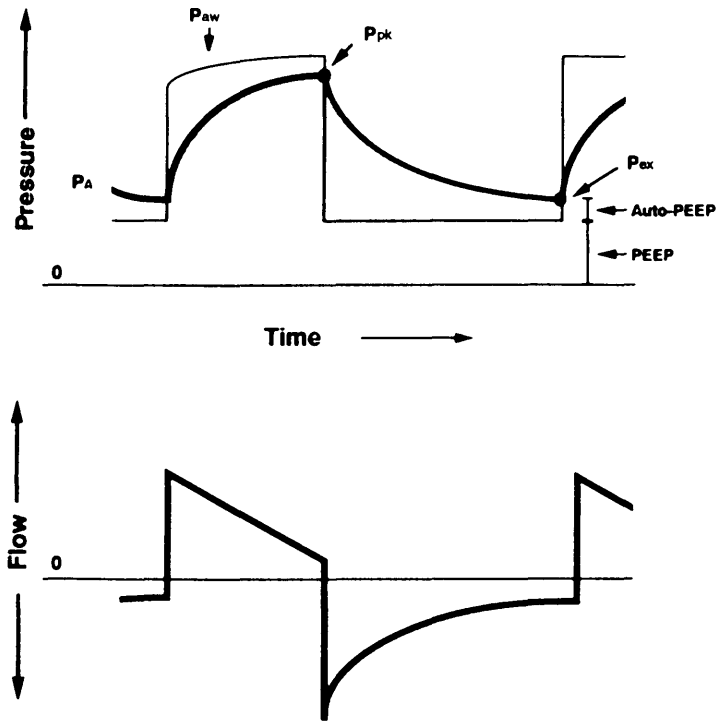


**Figure 1** Schematic diagram of airway pressure, alveolar pressure, and flow in a passive patient experiencing dynamic hyperinflation during volume cycled ventilation with decelerating flow. Total end-expiratory alveolar pressure ($P_{ex}$) is the sum of PEEP and auto-PEEP. Positive pressure drives expiratory flow until counterbalanced by pressure developed in the central airway by the next machine-delivered cycle. (From Ref. 27.)

eliminate auto-PEEP entirely. Even in the acute setting, auto-PEEP does not necessarily imply hyperinflation, as discussed below.

### *Determinants of Auto-Peep*

If no PEEP is applied, $P_{ex}$ is comprised solely of auto-PEEP, a dynamic pressure that may vary greatly from breath to breath during spontaneous breathing. It is also likely that auto-PEEP varies from region to region within the diseased lung under both passive and active breathing conditions (2). However, making the simplifying assumption that passive deflation occurs from a single compartment with no PEEP externally applied, the progressive reduction in alveolar pressure can be characterized to a first approximation as a uni-exponential function of the time

elapsed since the deflation onset (t), the end-inspiratory alveolar pressure ($P_s$), and the exhalation time constant ($t = R_xC = 1/k$):

$$P_{alv} = P_s\, e^{-kt} = P_s[e^{-t/RxC}]$$

[Here and in the subsequent equations, e is the numerical base of the natural logarithm system (2.7183).] At end-exhalation, t = te, and therefore:

$$P_{ex} = P_s[e^{-te/RxC}]$$

This last equation can be placed in clinical perspective by considering that $P_s$ is the sum of the tidal and residual elastic pressures. Accordingly, this expression can be rewritten:

$$P_{ex} = (P_{ex} + V_T/C)\, e^{-te/RxC}$$
$$P_{ex} = V_T/[C(e^{te/RxC} - 1)]$$
$$P_{ex} = V_E/[fC(e^{(1-z)60/fRxC} - 1)]$$

[Here, $f$, $V_T$, C, $T_E$, $R_X$, $\dot{V}_E$, and z represent frequency, tidal volume, compliance, expiratory time, expiratory resistance, minute ventilation, and the inspiratory time fraction ($t_i/t_{tot}$) of the respiratory system, respectively.] These equations indicate that auto-PEEP will be increased by a longer inspiratory time fraction, a longer expiratory time constant, or a greater minute ventilation. If $\dot{V}_E$, z, and all other inputs to this equation were to remain unchanged, auto-PEEP would not be strongly influenced by the pattern of breathing, i.e., the $f/V_T$ ratio would make little difference to its measured value (Fig. 2). Similarly, $P_{ex}$ does not appear to be greatly altered by changes in compliance. The same is not true of the *volume* "trapped" at end-exhalation, which for the same $P_{ex}$ is directly proportional to C. In the clinical setting, the effective expiratory time constant may well vary with the breathing pattern and minute ventilation. Nonetheless, the simplified mathematical formulas just given succinctly describe interrelationships that are potentially useful in the daily management of patients with severe airflow obstruction.

### *Types of Auto-PEEP*

#### Auto-PEEP without Proportionate Hyperinflation

Because auto-PEEP reflects only alveolar pressure ($P_{alv}$) and not *transalveolar* pressure (the difference between alveolar and pleural pressures), it is possible to have auto-PEEP without hyperinflation. This happens when expiratory muscle effort displaces the respiratory system from the equilibrium position appropriate to that alveolar pressure during complete muscle relaxation. Indeed, during exertion or when breathing against moderately high PEEP, many normal subjects strive to prevent or limit PEEP-induced chest distension, even when breathing quietly (3). Healthy persons routinely force the system below its equilibrium

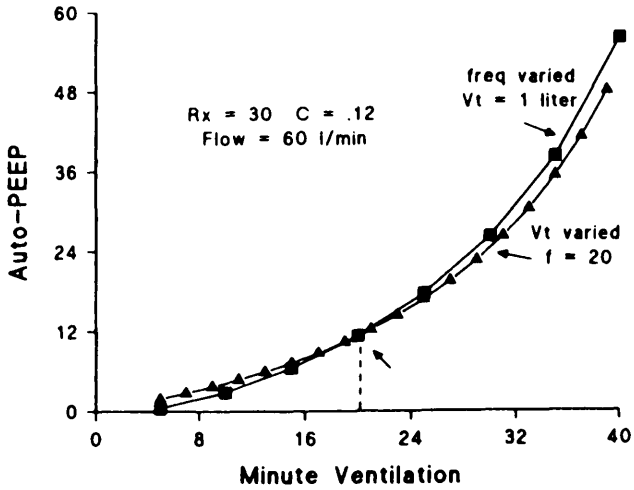


**Figure 2** Computer simulation of different breathing patterns on auto-PEEP during constant flow, volume cycled ventilation in a single compartment respiratory system. The curvilinear nature of these auto-PEEP/$\dot{V}_E$ relationships is due to the increasing $t_I/t_{TOT}$ which develops as minute ventilation at a fixed inspiratory flow rate. For a given minute ventilation, the magnitude of auto-PEEP does not depend strongly on the precise values of tidal volume or frequency. (From Ref. 59.)

position during upright exercise (4), and in patients without tidal limitation of expiratory airflow, compressing the chest against PEEP may be a method of sharing the inspiratory workload with the expiratory muscles (5). It has been demonstrated that increased gastric pressure explains much of the increment in end-expiratory alveolar pressure that occurs during spontaneous breathing in patients with chronic airflow obstruction (6), suggesting an important contribution of muscular effort to auto-PEEP in this setting.

### Auto-PEEP with Hyperinflation

Expiratory narrowing of the airway may be structural, functional, or both. With primarily structural narrowing and modest ventilatory requirements, e.g., mild asthma, there may be little tendency for expiratory airway collapse. Dissipated pressure losses ($P_R$) depend on flow rate, which itself is a function of minute ventilation, inspiratory time fraction, and the pressure-flow relationship of the exhalation pathway: $P_R = k\dot{V}^{\epsilon}$. During purely laminar flow, $\epsilon = 1$, and during fully developed turbulent flow, $\epsilon = 2$. $P_R$ for exhalation is the driving pressure for expiratory flow, i.e., the difference between alveolar and atmospheric pressures.

As $\dot{V}E$ rises, the inspiratory time fraction has an increasingly important influence on the average expiratory flow rate, on computed values for airway resistance, and on the average pressure drop across the airway. Auto-PEEP detected in patients without intrinsic airway disease often originates primarily at the level of the expiratory valve, the resistance of which rises as a function of the average flow across it: $[\dot{V}E/(1 - (t_i/t_{tot})]$. Expiratory valve resistance, in conjunction with endotracheal tube impedance, a reduced number of patent airways, and expiratory muscle action, helps to account for the high incidence of "auto-PEEP" reported in the acute respiratory distress syndrome (ARDS)—inherently a *restrictive* disease (7).

When the airway collapses during (passive or active) tidal deflation, flow limitation may occur similar to that experienced during forced spirometry. Expiratory effort intensifies the obstruction, often tending to accentuate air trapping, rather than to speed deflation. It is likely that flow-limited and non-flow-limited exhalation pathways exist in parallel within the obstructed lung, along with marked interregional differences in air trapping. The presence or absence of dynamic airway compression and flow limitation has significant implications for the therapeutic management of such patients.

In the nonpassive subject, auto-PEEP is highly variable both with regard to its distribution within the lung and with respect to its dynamic average value. The interregional variation of auto-PEEP may be particularly wide in patients with acute asthma. That many airways are occluded during severe asthma attacks has been suspected for many years. It is not commonly taken into account, however, that extensive regional occlusion may prevent accurate end-expiratory assessment of the degree of air trapping present. In such cases, the end-*inspiratory* plateau pressure may better track variations in lung volume (8). Because auto-PEEP is a sensitive function of minute ventilation, changes in breathing frequency can cause marked changes of auto-PEEP in patients who vary this parameter.

### *Physiological Consequences of Dynamic Hyperinflation*

Dynamic hyperinflation often contributes to the protracted ventilator dependence of patients with airflow obstruction. Failure to address auto-PEEP may lead to significant management errors, increased breathing effort, and/or hemodynamic compromise.

#### Breathing Effort

*Work of Breathing.* Dynamic hyperinflation implies a higher position on the pressure-volume curve of the respiratory system. This distension tends to increase airway caliber but reduce compliance. The total elastic pressure required to inspire a given tidal volume rises for two reasons: first, the hyperinflated system has increased stiffness, and second, auto-PEEP represents an expiratory bias or threshold pressure that must be overcome to initiate inspiration (9). This expiratory bias

pressure may be sufficiently high to impede or prevent triggering of the ventilator during the machine-aided cycles of assist/control ventilation, synchronized intermittent mandatory ventilation (SIMV), or pressure support (Fig. 3). Auto-PEEP not only impairs the triggering of machine-assisted cycles, but also interferes with the ventilatory effectiveness of spontaneous breaths and of pressure preset (pressure control or pressure support) ventilation (Fig. 4). The latter may be partially offset by PEEP added to the airway opening (10).

*Respiratory Muscle Function.* Dynamic hyperinflation compromises the pumping action of the ventilatory system (11). Acute hyperinflation shortens the resting length of the inspiratory muscle fibers (reducing preload) and alters the configuration of muscle groups that must interact effectively to power inspiration. As the diaphragm flattens, it loses its "zone of apposition" with the lowermost

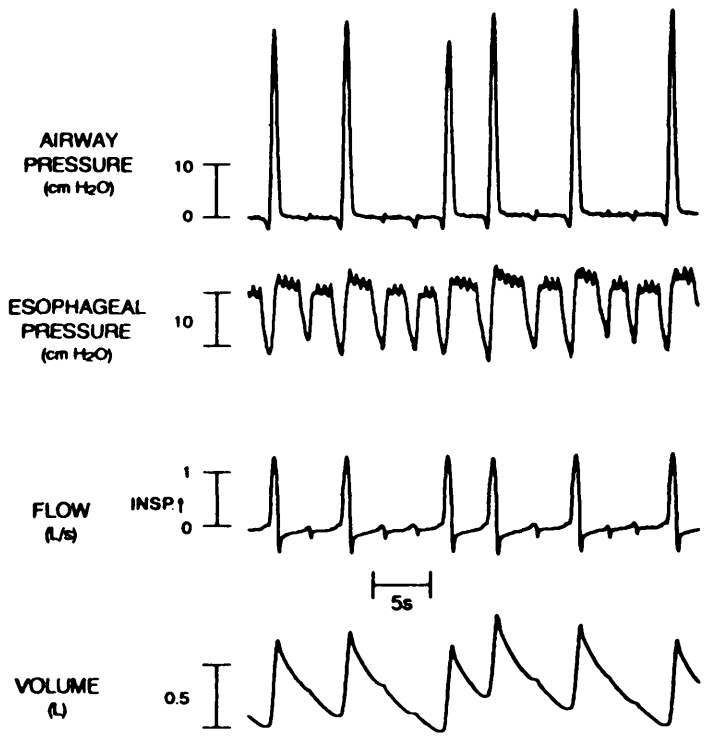


**Figure 3** Experimental record demonstrating triggering inhibition during assist-controlled ventilation in a patient with severe chronic airflow obstruction and dynamic hyperinflation. Note the cycle-to-cycle variation in lung volume. (From Ref. 60.)

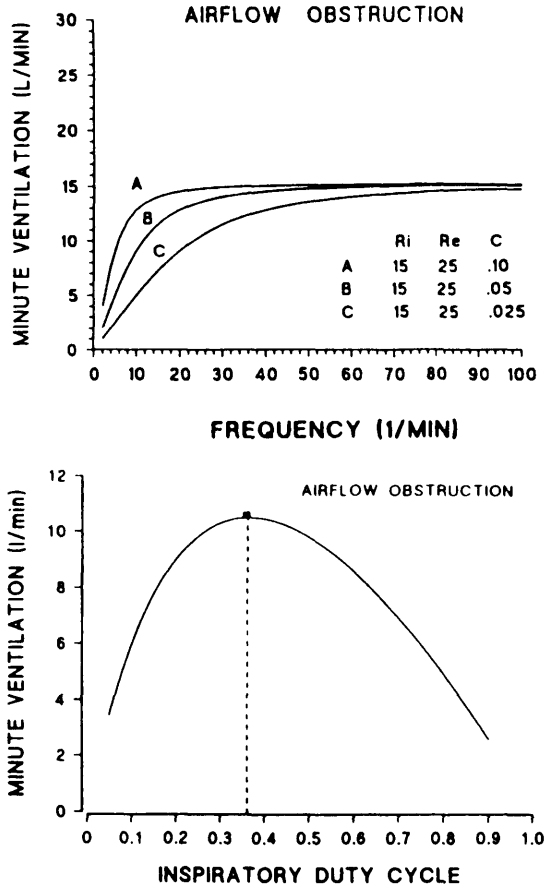


**Figure 4** Influence on minute ventilation of frequency (top) and inspiratory duty cycle (bottom) during pressure-controlled ventilation of a patient with severe airflow obstruction. (Top) Note that for a given level of applied pressure there is a distinct upper bounding limit for minute ventilation as frequency increases. Compliance affects the minute ventilation observed at any given frequency, but does not influence the bounding limit itself. Optimal ventilatory efficiency is normally achieved at slow frequencies. (Bottom) In a typical flow-obstructed patient, there is a well-defined optimum duty cycle needed to achieve a given minute ventilation for the same applied pressure. (From Ref. 47.)

rib cage, so that positive intraabdominal pressures generated during inspiration do not flare the lower ribs to produce the normal inspiratory action (12). Furthermore, the horizontal orientation of the diaphragmatic muscle fibers tends to convert phasic tension into an *expiratory* rather than inspiratory force vector. Conversely, the extradiaphragmatic respiratory muscles become increasingly important in accomplishing inspiration, because they lose relatively little of their precontractile length and inherent strength at high volumes. The compliance of the distended chest wall declines at high lung volumes (greater than ≈60% of vital capacity), as inwardly directed recoil of the chest cage supplants the outwardly directed recoil that normally assists inspiration at lower lung volumes. How important these latter changes are during *chronic* ventilatory compromise is presently an unsettled question (12).

The relative importance of the nondiaphragmatic ventilatory musculature in breathing during hyperinflation helps to account for two commonly observed phenomena. First, the key role of the skeletal ("postural") muscles of the thoracic cage in stabilizing the thorax for optimal breathing efficiency may account for the dyspnea experienced by many such patients when arm activity diverts their contractile power to other uses (13). Consequently, patients with extreme hyperinflation may become seriously dyspneic with activities of daily living that involve arm extension. Second, the diaphragm is normally of pivotal importance during sleep, especially in the rapid eye movement (REM) stage. During REM, the activity of extradiaphragmatic muscles is significantly inhibited (14), and the diaphragm tends to bear a greater portion of the breathing workload. Because diaphragmatic contraction is usually ineffective in severe COPD, relative hypoventilation may occur during these periods, with resulting hypoxemia and possible sleep disruption (15). Such disturbances may be instrumental to the evolution of decompensation or to the failure of attempted ventilator withdrawal.

### Hemodynamic Importance of Dynamic Hyperinflation

Raising mean right atrial pressure relative to that in the systemic vasculature impedes venous return (16). As dynamic hyperinflation develops under passive conditions, mean alveolar pressure must rise because distension of the lung and passive chest wall requires a positive distending force. This rise, in turn, causes mean pleural and right atrial pressures to increase. Quite different dynamics prevail during spontaneous breathing. Here, *net* intrathoracic pressure often *falls* as the vigor of inspiratory effort increases. Simultaneously, *end-expiratory* intrathoracic pressure may remain stable, decline slightly, or, more commonly, rise to a higher level. Although these relationships were first described in studies of spontaneously breathing asthmatic children (17), similar observations have also been made in adult patients with COPD being weaned from ventilatory support (18) (Fig. 5). Cardiovascular stress tends to occur during sudden transitions from mechanical ventilation to spontaneous breathing. Spontaneously breathing pa-

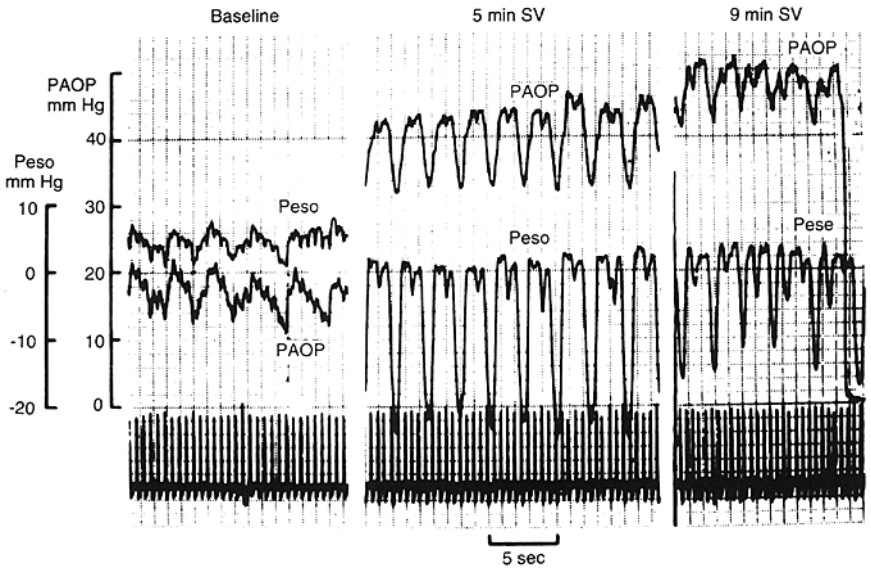


**Figure 5** Changes in esophageal ($P_{ESO}$) and in wedge pressure (PAOP) during a brief trial of spontaneous breathing in a patient with COPD and cardiac dysfunction. As the transition is made from full ventilator support (baseline) to spontaneous ventilation (SV), wedge pressure rises dramatically and mean esophageal pressure falls. Note that end-expiratory esophageal pressure falls modestly at first, and then begins to rise as the patient fatigues. (From Ref. 18.)

tients with auto-PEEP are more at risk for right heart decompensation (due to the increased right ventricular afterload which accompanies hyperinflation), for alveolar flooding (due to increased venous return and higher cardiac output), or for left heart compromise (due to ischemia, diastolic dysfunction, or increased afterload) than for falling venous return. The increased work of breathing may cause cardiac strain on that basis as well.

An acute depression of cardiac output is frequently precipitated when mechanical ventilation is initiated in patients with severe airflow obstruction (19). As sedatives and paralytics are given to establish passive conditions, mean intrathoracic pressure rises, tending to impede venous return. At the same time, vascular compensatory mechanisms that normally tend to preserve the gradient driving venous return are blunted by pharmacological vasodilation in conjunction with elimination of skeletal muscle tone and phasic respiratory pumping. It is not uncommon, therefore, for hypotension to occur in the recently intubated patient with COPD. Indeed, apparent electromechanical dissociation secondary to auto-

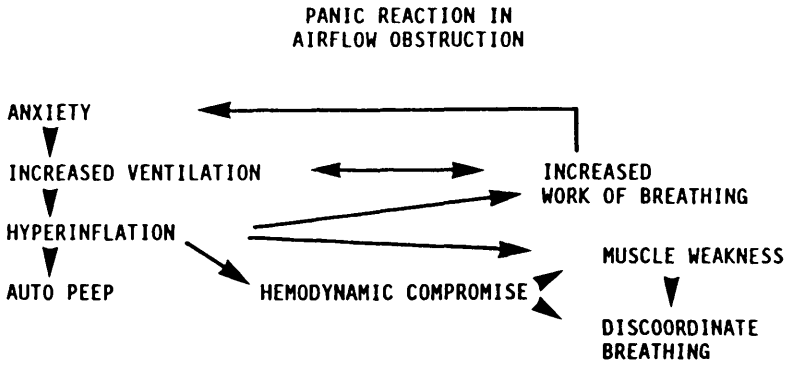


**Figure 6** Positive feedback "panic cycle" often observed in patients with severe airflow obstruction and accentuated minute requirements.

PEEP has been reported during cardiopulmonary resuscitation. In the presence of auto-PEEP, measured central venous (CVP) and pulmonary artery occlusion (wedge) pressures may be misleadingly high (19,20).

### The "Panic" Cycle

Knowing the problems inherent to dynamic hyperinflation, it is not surprising that seriously obstructed patients often enter a "panic" cycle whenever increased minute ventilation or respiratory impedance elicit forceful breathing (Fig. 6). This increased breathing effort itself increases $\dot{V}O_2$ and $\dot{V}CO_2$. As a rising ventilation requirement accentuates dynamic hyperinflation and auto-PEEP, work per liter of ventilation as well as the number of liters of ventilation required per minute both increase. Simultaneously, acute hyperinflation impairs the action of the thoracic pump. Central vascular congestion and ventricular ischemia may further compromise muscular efficiency, boost the breathing workload, increase anxiety, and contribute to discoordinate breathing. This self-reinforcing cycle can often be broken by verbal coaching, enhanced ventilatory support, or timely reduction of anxiety, airway resistance, or the $\dot{V}E$ requirement. Sudden transitions between levels of ventilatory support are particularly likely to precipitate problems—a fact that argues against the use of intermittent "t-piece" or "blow-by" periods as a weaning method in patients with marginal reserve. For some patients, appropriate cardiovascular therapy may be a crucial adjunct.

## II. Practical Management of Airflow Obstruction

The foregoing discussion provides important background information needed to develop an appropriate strategy for the ventilatory management of patients with

severe airflow obstruction. Nutrition, infection management, secretion clearance, bronchodilation, airway humidification, and skillful fluid-electrolyte management are key elements in the therapeutic scheme. Three areas deserve special mention: cardiovascular function during mechanical ventilation, sedation and paralysis, and circuit configuration.

### A. Cardiovascular Function and Mechanical Ventilation in Airflow Obstruction

Relief of the very high breathing workload associated with severe airflow obstruction by effective mechanical support allows a parallel reduction of $\dot{V}O_2$ and the associated requirement for cardiac output (21). Such energy savings can make a crucial difference to the patient with stressed or inadequate cardiovascular reserve. Once effective ventilatory support is provided, sudden resumption of a high breathing workload can precipitate coronary ischemia, diastolic dysfunction, and pulmonary vascular congestion (Fig. 5) (18). In some patients, the strain produced by alveolar hypoxia and lung overdistension results in right heart dilation, left ventricular crowding (via cardiac interdependence), and consequent pulmonary vascular congestion.

Although adequate ventilatory support aids ventricular function, it is important to proceed cautiously, not giving more than is needed to ensure comfort and acceptable blood gases. Providing more ventilatory support than needed may accentuate dynamic hyperinflation.

### B. Sedation and Paralysis

Sedation, complemented by pharmacological paralysis when necessary, may be required in the early stages of ventilatory support to allow well-coordinated mechanical ventilation and effective muscle rest. As a general rule, 12–72 hours of deep sedation or paralysis are appropriate to rest the ventilatory muscles, to assure sleep quality, and to provide sufficient time for initial therapy to reverse the problem precipitating decompensation. Yet, after 24–48 hours of complete rest, deconditioning and protein catabolism are well underway. Furthermore, silencing of muscular effort eliminates coughing and encourages retention of airway secretions, especially in dependent areas. Certain neuromuscular blocking agents may result in prolonged weakness (22,23) or overt neuromyopathy, particularly when used in conjunction with corticosteroids (24). Anxiolytics may overcome the stimulating effects of bronchodilators and corticosteroids and therefore help to achieve adequate rest.

### C. The Ventilator Circuit

During acute exacerbations of airflow obstruction, the primary site of expiratory flow resistance usually resides in the small airways (<2 mm in diameter). None-

theless, care should be taken to insert a tube of appropriate diameter so as to facilitate the extraction of airway secretions by suctioning. Sufficient pressure support should be provided to offset endotracheal tube resistance during spontaneous breathing cycles (25). The pressure level should be monitored and frequently readjusted, however, to provide adequate support without causing overdistension or impeded exhalation (see below). The impact of resistive circuit elements (expiratory valves, endotracheal tube) will vary with flow demands and breathing frequency. Although moderate flow retardation can benefit patients who are flow-limited during tidal breathing, high expiratory resistance through the endotracheal tube or expiratory valve can increase dyspnea, even if increased air trapping does not result.

## III. Partial Ventilatory Support

In the present clinical setting, the primary options for partial ventilatory support include assist-control ventilation, pressure-control (time-cycled) ventilation (PCV), synchronized intermittent mandatory ventilation (SIMV), pressure support ventilation (PSV), continuous positive airway pressure (CPAP), and newer modes that combine features of pressure-assisted and volume-guaranteed machine cycles. Certain options, such as CPAP, pressure support, and proportional assist ventilation may be particularly well adapted to noninvasive support.

### A. Assist Control

Volume-controlled, flow-limited assist ventilation is the primary mode applied by many clinicians in the initial phase of acute support. Here, a relatively rapid inspiratory flow setting is selected (≈4–6 times the minute ventilation requirement) in order to minimize end-expiratory gas trapping. Early on, moderate sedation is often required to avoid overt dyssynchrony between patient and machine. Should inspiratory flow prove inadequate or the patient experience dyspnea for other reasons (e.g., depressed *effective* triggering sensitivity due to auto-PEEP), considerable inspiratory work may be experienced, despite machine assistance (26). The decelerating flow waveform (27) may improve gas distribution among heterogeneously affected lung units. Using modest levels of PEEP in patients with expiratory flow limitation may decrease dyspnea that arises secondary to dynamic collapse of central airways (28), as well as improve the threshold for initiating inspiration (10,29).

### B. Pressure Control

PCV appears to have a rather limited place in the clinical management of patients with serious airflow obstruction. The ventilatory efficiency of PCV is dramatically influenced by the frequent changes in airflow impedance, chest wall compliance,

and auto-PEEP that characterize such patients. Moreover, the ventilation of patients with severe airflow obstruction is markedly affected by the clinician's choice of frequency and $t_i/t_{tot}$ (Fig. 4) (30). As for pressure support ventilation, adding PEEP to offset auto-PEEP may improve the tidal volume afforded by PCV. For these reasons, minute ventilation and blood gases should be monitored closely when PCV is employed.

### C. Pressure Support

PSV aids greatly in overcoming endotracheal tube resistance and should be routinely employed for this purpose for intubated patients who take spontaneous breaths. It should be recognized, however, that the resistance of the upper airway may increase immediately after extubation to values higher than those faced prior to extubation (31) (Fig. 7). The reason is unknown, but inflammation and edema of the tissues forming the soft palate or upper airway may be important. For such postextubation problems, the temporary institution of CPAP or noninvasive ventilation may be helpful.

PSV used as a "stand-alone" power source and mode for weaning presents a number of advantages and potential problems for the patient with severe airflow

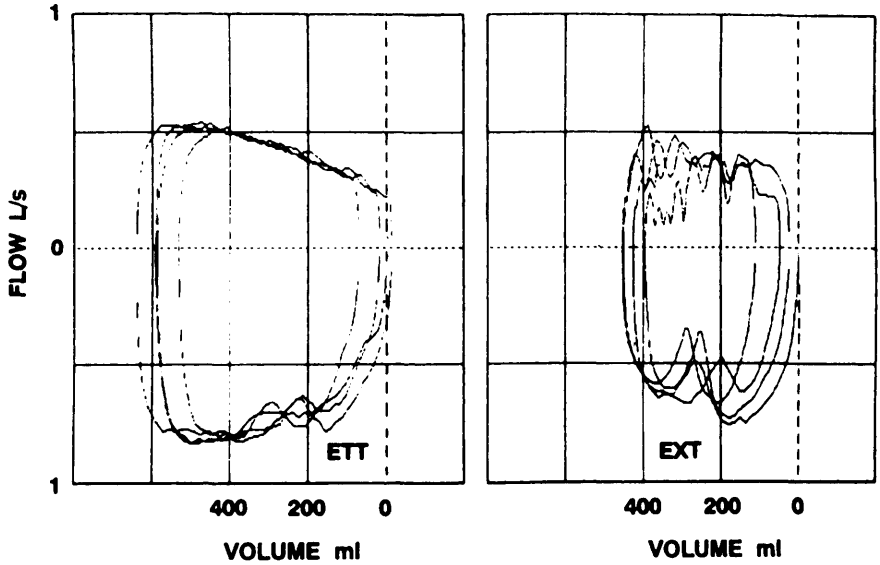


**Figure 7** Flow-volume loops recorded before (left panel) and after (right panel) endotracheal extubation. Note the blunted and irregular contours of the postextubation profiles of upper airway obstruction. (From Ref. 31.)

obstruction. The provision of moderate PSV offsets tube resistance and provides some ventilatory support to the patient during sleep. However, like PCV and other forms of pressure-limited ventilation, its ventilatory efficiency is susceptible to fluctuations of lung and chest wall compliance. Secretions, bronchospasm, and increases of chest wall muscle tone all interfere with PSV effectiveness. Auto-PEEP that develops or increases (e.g., as part of a panic cycle or due to increased airway resistance) effectively negates a portion of the applied PSV, forcing the patient to inspire with greater effort (Fig. 8). (Adding PEEP can improve the ventilatory efficiency of a fixed level of pressure support.) Moreover, most PSV circuits cannot keep pace with the timing or vigor of forceful inspiratory efforts, especially at rapid breathing frequencies or when no CPAP is used to help improve effective triggering sensitivity. Such limitations may be partially overcome by increasing the PSV level. However, high fixed levels of PSV can be problematic when the majority of the pressure dissipates against flow. Because the respiratory system of most patients with airflow obstruction is relatively compliant, over-distension and discomfort may arise at the higher PSV level when the patient calms sufficiently to reduce $\dot{V}_E$. As minute ventilation falls, so do flow resistive

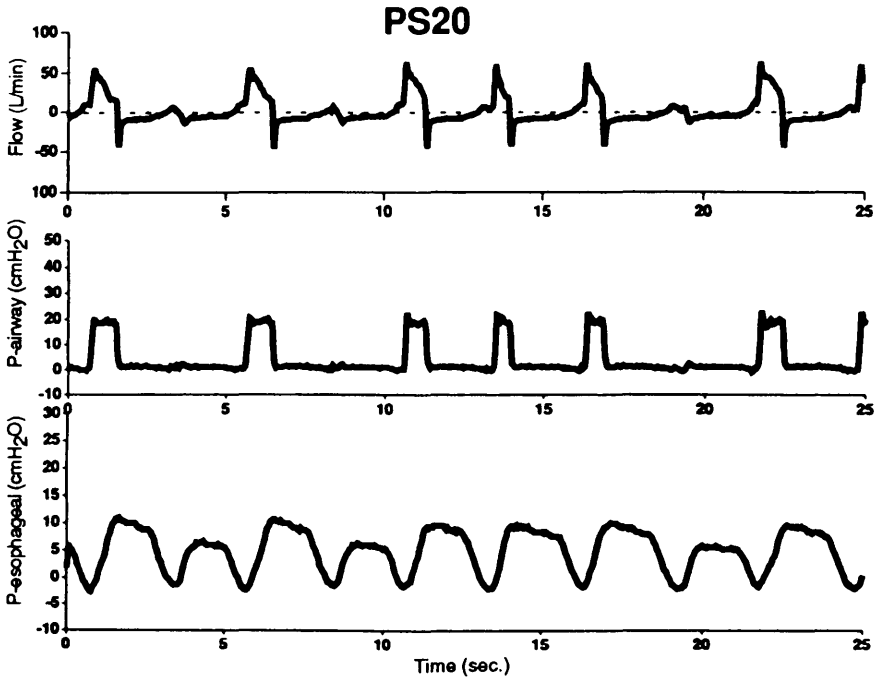


**Figure 8** Failure of inspiratory effort to initiate pressure support, due to auto-PEEP.

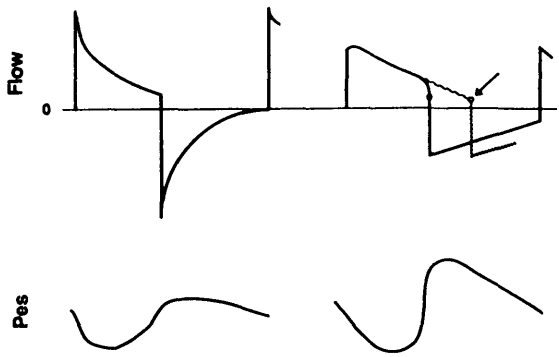


**Figure 9** An inspiratory flow of a specified value or of a specified percentage of the peak value provides the signal for the ventilator to stop pressurizing the airway during pressure support. Because patients with airflow obstruction or those breathing through a narrow endotracheal tube have a rectilinear flow profile, active expiratory effort may be required to initiate expiration.

pressure losses. Therefore, increased elastic forces and uncomfortable tidal volumes could theoretically be generated when such countermeasures are taken.

As discussed below, the patient with severe COPD who receives PSV is often obligated to *actively* signal the machine to end the inflation cycle (Fig. 9) (32). Because the inspiratory flow profile is rather rectilinear, it fails to decay to the requisite off-trigger value within a time frame consistent with length of the inspiratory duty cycle set by the patient's own respiratory drive center. Under passive conditions, auto-PEEP can actually *increase* as pressure support is augmented, both because the $\dot{V}_E$ may rise and because delayed "off-switching" effectively lengthens $t_i/t_{tot}$ and shortens $t_e/t_{tot}$. Unlike the patient receiving SIMV, the patient receiving PSV can defer acceptance of the workload as the supporting pressure is withdrawn simply by increasing breathing frequency. Total machine power provided per minute may remain approximately constant over a wide range. Therefore, the rate at which the ventilatory muscles are reloaded accelerates with the final few decrements of supporting pressure (33,34).

Failure to trigger a pressure-supported cycle can occur whenever the lung volume is too great to allow the inspiratory effort to overcome the combination of auto-PEEP and the set trigger criterion (Fig. 8). When moderately high PSV levels are used, intermittent failure to pressurize the spontaneous cycle often results. This may occur because less effort is expended or because each effort is less effective. In either event, reducing the PSV may actually improve synchrony between patient effort and machine response, because as the patient works harder, each forceful effort succeeds in overcoming the effective threshold.

Despite these major shortcomings, PSV does have a defined place as a primary power source for the patient with COPD who has relatively few secretions, stable ventilatory drive, a modest $\dot{V}E$, and only moderate severity of illness. When properly adjusted, PSV often proves more comfortable than SIMV as a support technique.

### D. Synchronized Intermittent Mandatory Ventilation

Properly adjusted SIMV can be a comfortable mode of ventilation that results in less overt pressure-limiting dyssynchrony than assist/control ventilation. Yet many of the problems of triggering dyssynchrony that occur with PSV also occur with SIMV, and for similar reasons. SIMV should virtually always be combined with "low-level" CPAP and "low-level" PSV to optimize the triggering characteristics of the spontaneous and machine-assisted cycles, as well as to offset endotracheal tube resistance (Fig. 10). Some cycle-to-cycle variation of patient effort is expected for quiet and moderately vigorous breathing during SIMV. However, it is noteworthy that in the dyspneic patient, effort (assessed by the inspiratory time product) may not vary greatly cycle to cycle at any given level of machine support (35). Below about 50% of the assisted ventilation frequency, effort per tidal cycle may be essentially the same as for spontaneous breathing. In this limited sense, SIMV resembles pressure support, a mode in which there is great similarity among the effort profiles of contiguous breaths. Levels of dyspnea and anxiety also may not vary greatly between PSV and SIMV at similar levels of

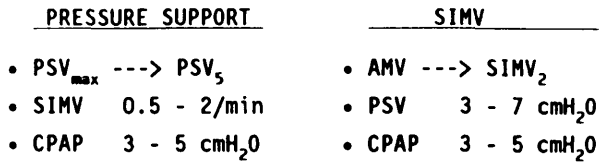


**Figure 10** Two alternatives for weaning from mechanical ventilation. In both instances, a similar strategy is followed. Priority is given to (1) overcoming endotracheal tube resistance with pressure support during each spontaneous breathing cycle, (2) ensuring periodic large breaths (with SIMV) for volume recruitment and reversal of atelectasis, (3) maintaining a sufficient end-expiratory lung volume with low-level CPAP, and (4) providing ventilatory support adequate for high-quality sleep. When pressure support is used as the primary source of machine power, it is varied from $PSV_{max}$ (providing a large tidal volume of approximately 7–10 ml/kg) to a value of 5 $cmH_2O$. Marginal patients are required to demonstrate the ability to breathe comfortably through the endotracheal tube without pressure support for 1–2 hours prior to extubation. When SIMV is used for this purpose, the frequency of machine cycles is tapered from every breath (assist control, AMV) to two breaths per minute.

machine-delivered power (36). However, as already noted, SIMV tends to reload the respiratory system earlier in the course of ventilator weaning than does PSV.

### E. Airflow Obstruction and Ventilator Synchrony

During partial ventilatory support, the ventilator should act as an auxiliary power source whose magnitude is adjustable by the physician and subject to the command of the patient's ventilatory control center. Optimal synchrony would allow perfect coordination of cycle onset and cycle offset, with power provided in an appropriate intensity and pattern for patient comfort. Several aspects of severe airflow obstruction, however, contribute to poor coordination between patient and machine. When dynamic hyperinflation occurs, the patient experiences a relative inability to initiate machine cycles. This is particularly true when relatively high levels of pressure support or large tidal volumes are used in SIMV. In the setting of expiratory flow limitation, adding PEEP to the external airway will simply narrow the difference between alveolar and central airway pressures until some critical pressure is exceeded. For many patients, this critical pressure appears to average about 80–85% of the original auto-PEEP value without PEEP applied (10,37). (Auto-PEEP itself is a composite "average" value.) In theory, the PEEP necessary to offset the impediment to triggering may be somewhat less than the average value for critical pressure, as only the auto-PEEP of the least affected units must be overcome. When pressure support is in use, the addition of PEEP can dramatically improve the tidal volume associated with any fixed level of support.

Not only is triggering sensitivity impaired by the auto-PEEP associated with severe airflow obstruction, but, as already noted, the off-switch to inflation may also be difficult to signal. Clearly this is true when constant flow and fixed tidal volumes are used in a patient with variable requirements receiving volume-cycled ventilation, as reflected in the variation of peak inflation pressure. It is less commonly appreciated that off-switch asynchrony occurs during pressure support ventilation as well. The algorithm used by most ventilators with pressure support requires that a fixed low level of flow or a fixed percentage of the peak flow value be sensed before the machine stops pressurizing the airway. When there is severe inspiratory airflow obstruction (secondary to a narrow endotracheal tube or intrinsic airways disease), the flow profile becomes less decelerating—even in response to a perfectly square wave of inspiratory pressure (Fig. 9). This difficulty in triggering the off-switch is particularly likely to occur when high levels of pressure support are used, as the resulting flow profile progressively resembles a square wave of flow under these circumstances. Thus, both inspiratory and expiratory difficulty may be encountered. It is also important to understand that the power provided by PSV deteriorates markedly as frequency increases. For all of these reasons, high-level pressure support often proves ineffective or suboptimal for patients with large work requirements and severe airflow obstruction.

### F. Proportional Assist Ventilation

In the near future, many of the drawbacks of PSV just mentioned may be avoidable with a newly described technique of partial ventilatory assistance, termed proportional assist ventilation (PAV) (38,39). The basic idea behind PAV is that the ventilator should act as an auxiliary set of muscles whose output varies in direct proportion to patient effort (Fig. 11). Although the clinician selects the amplification intensity and character of this "auxiliary support," all timing and depth components of the breathing cycle are under direct patient control—a feature that should help assure patient-ventilator synchrony for the cycle onset and off-switch signals. PAV derives its sensitivity to varying pressure demands from information gathered by monitoring flow and volume. By adjusting independent gains for flow and volume, the clinician is able to adjust the overall proportionality constant or amplification factor (power assist) as well as determine how the machine's assistance is partitioned across the elastic and nonelastic impedance elements defined by the equation of motion. Although PAV is an exciting new concept that has features especially attractive to the management of patients with severe airflow obstruction, it is currently unproven and undergoing clinical evaluation. Nonetheless, such delicate flow control and flexible power assist may eventually improve the ease with which machine support may be withdrawn.

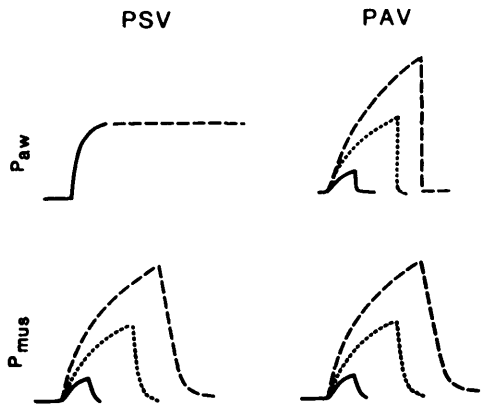


**Figure 11** Conceptual difference between pressure support ventilation (PSV) and proportional assist ventilation (PAV). As muscular pressures generated by the patient vary, note that pressure support and proportional assist respond differently. During PSV, $P_{aw}$ remains constant, so that the delivered flow and volume may be quite different—greater or less—than those needed by or acceptable to the patient. With PAV, airway pressure remains proportional to muscular effort at all points in the inspiratory cycle. (From Ref. 40.)

### G. Noninvasive Ventilation

The potential for noninvasive ventilatory support (NIV), applied continuously for extended periods or intermittently on a continuing basis, is only now being extensively explored. The concept of using noninvasive ventilatory assistance with positive pressure was originally developed to facilitate the application of CPAP for treatment of obstructive sleep apnea. As a broad extension of that successful experience, numerous pressure- and volume-based modes of ventilatory assistance can now be applied using a tightly fitted facial mask or occlusive nasal appliance to deliver modest airway pressures (generally less than 25 $cmH_2O$). Benefits in terms of improved blood gases and/or reduced effort are clearly demonstrable during the period of pressure application. Recent studies have strongly suggested the value of NIV as a temporizing measure to avert intubation or facilitate extubation in acutely ill subjects (41,42). (The success with which it is applied, however, varies considerably from center to center.) Furthermore, a growing number of studies now indicate that benefits persist well after the end of the individual ventilation period (43,44). Reduced dyspnea and increased activity levels, in association with improved blood gases (while unsupported), enhanced muscle strength, and improved sleep quality have been reported in various investigations of patients with neuromuscular weakness or COPD. Controversy persists, however, regarding the long-term benefit of NIV in these patients.

The use of nocturnal nasal ventilation in patients with chronic airflow obstruction is especially intriguing. Because patients with severe airflow obstruction depend heavily on the intact function of the extradiaphragmatic musculature, provision of adequate ventilatory assistance during sleep may improve sleep quality and preserve adequate blood gases. These benefits may help explain recent enthusiastic reports regarding this technique as an adjunct for both inpatient and outpatient use (41,42). Such reports also lend rationality to the practice of providing increased ventilatory support during sleep periods in all intubated, hospitalized, ventilator-dependent patients.

Unfortunately, the experience with NIV has not been uniformly positive. There is a general consensus that patients with very severe airflow obstruction and a high load of secretions are poor candidates for this type of assistance (45). Compliance of the patient is a difficult problem, and congestion of the nasal passages severely impairs the effectiveness of nasal ventilation support. Many (if not most) patients cannot tolerate more than 12–15 $cmH_2O$ of inspiratory airway pressure. Nasal pressure may also increase nasal discharge.

Various forms of noninvasive support using negative pressure ventilation have also been developed, ranging from tank ventilation to chest wall oscillators. These devices have also been employed successfully for specific indications. At present, however, it remains unclear whether any are of lasting value for chronic application in ambulatory patients with severe airflow obstruction.

Pressure-limited modes of ventilatory support, such as biphasic airway pressure (Bi-PAP) and airway pressure release ventilation (APRV), a mode with similar characteristics (46), tend to compensate well for moderate leaks that develop between appliance and patient but are inherently limited in their ability to ventilate the patient with serious airflow obstruction. To give adequate support, pressures are sometimes required exceeding those that can be comfortably applied (generally $<20$ cm$H_2O$). Moreover, circuit leaks commonly develop. The efficacy of ventilation relies on the exponential buildup and decay of alveolar pressure and volume, a process retarded by airflow obstruction (30,47). Despite the great potential value of NIV, much remains to be proven before a place is confirmed for these techniques in patient care. Nonetheless, reports now emerging strongly suggest the benefit of these adjuncts for well-selected patients.

NIV provided by full face mask has numerous applications in the acute care setting. These include management of exacerbated airflow obstruction without intubation and application as a "bridging" measure in the immediate postextubation period (48). Although somewhat less comfortable than nasal masks, full face masks tend to work as well or better for such patients, especially in the setting of nasal congestion (where much of the applied pressure dissipates against nasal resistance). Whichever mask type is chosen, patients with copious airway secretions tend to respond poorly. Whatever technique is used, intensive coaching and readjustment of the apparatus is necessary during the initial period to achieve a satisfactory result. Improvement, as gauged by improved ABGs or comfort, is usually evident within the first 2 hours.

## IV. Weaning from Ventilatory Support

Although it is rather easy to predict the success or failure of a weaning attempt in the majority of cases, the prediction of outcome is much more difficult in some. Clearly, the development of cardiac failure, coronary ischemia, severe arterial hypoxemia, psychogenic decompensation, and other "nonventilatory" problems can perpetuate machine dependence. These are somewhat difficult, however, to quantify or incorporate into meaningful predictive indices for success or failure. It has become clear that even for ventilatory insufficiency, isolated measures of workload (e.g., $\dot{V}_E$) or muscle strength [e.g., maximal inspiratory pressure (MIP)] have only limited value. This may be due to the fact that the ventilatory pump and the neural center that controls it interact closely in an attempt to avoid both $CO_2$ retention and catastrophic muscle fatigue (49). The most successful weaning indexes, therefore, seem to take the ratio between power requirement and power output reserve into account, either indirectly through observations of involuntary patient response or by direct measurement (e.g., the ratio between the pressure required per breath and the MIP, the ratio of tidal volume to vital capacity, or the

ratio of $\dot{V}_E$ to maximum voluntary ventilation). Involuntary measures such as the $P_{0.1}$ (50,51) and the $CO_2$-stimulated $P_{0.1}$ (52) hold promise, but at present remain technically difficult for routine use. Similarly, complex scoring systems seem to work well in a research setting (53), but are difficult to implement in practice. Quantitative assessment of the breathing rhythm (e.g., using the $f$ to $V_T$ ratio) and semiquantitative characterization of the pattern of muscle activation and muscular coordination in response to imposed stress (54,55) may offer an effective clinical compromise for the clinical setting.

In recent years, a great deal has been written regarding the serious problem of protracted ventilator dependence in patients with airflow obstruction. Certain modes have been suggested as preferable to others, often with little scientific information to substantiate these assertions. Patients with severe airflow obstruction must be weaned gradually and with considerable skill in order to avoid panic reactions and adverse cardiovascular consequences as well as to allow gradual readaptation to the ongoing stress of tidal breathing (56).

As noted earlier, there are clear differences between SIMV and pressure support, the two most widely employed methods of partial ventilatory assistance. When used alone, SIMV tends to reload the respiratory system abruptly over a restricted range of machine support that usually corresponds to 25–50% of that provided during AMV. Conversely, weak patients tend to respond to a declining level of PSV by increasing frequency, thereby deferring the reloading of the respiratory system until the very last stages of withdrawing pressure support.

PSV also provides a measure of flexibility in that the patient can call on additional machine support during sleep or under conditions of ventilatory stress. At the same time, however, the support that PSV offers per cycle is limited. As a pressure-determined mode, the support provided by PSV varies with changes in airway resistance, respiratory system compliance, or auto-PEEP. Because these loading conditions tend to change rapidly in patients with bronchospasm, copious airway secretions, or variable minute ventilation requirements, PSV does not always provide reliable support. When PSV levels are low, very shallow tidal volumes may be taken, which result in atelectasis or reduced ventilatory efficiency. Under these circumstances, periodic inflation with large volume-cycled breath may be indicated. A low level of CPAP is generally justified to help avert atelectasis or to counterbalance auto-PEEP.

### A. Combination Modes for Assisted Ventilation

Certain newer forms of assisted ventilation regulate the applied pressure or supply supplemental flow as necessary to achieve the targeted tidal volume (57,58). Such features can be of value in overcoming some of the shortcomings of pressure support and pressure control in the management of patients with severe airflow

obstruction. Volume support, for example, monitors the tidal volume associated with the applied pressure and varies the pressure level accordingly. Failure to achieve the intended level is countered by additional help from the machine. Conversely, an excessive tidal volume prompts a reduction in the applied pressure value. Volume-assured pressure support ventilation is another approach to accomplishing the twin objectives of allowing a generous amount of patient control of the cycling rhythm while guaranteeing an appropriate tidal volume. Here, if the applied level of pressure support is insufficient to achieve the tidal volume intended, a flow generator operating in parallel completes the task, albeit at the cost of determining the patient's flow pattern and extending the inspiratory time (Fig. 12). Although both modes are likely to represent an advance over conventional pressure support, they both have shortcomings that prevent their consideration as an ideal methodology.

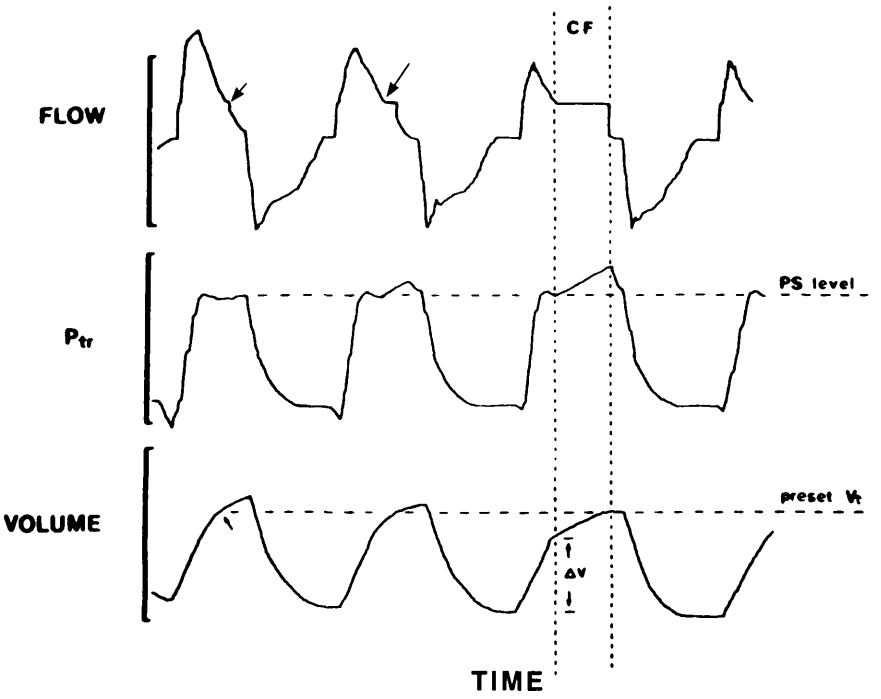


**Figure 12** Volume-assured pressure support ventilation for inadequate breathing efforts result in flow support from the ventilator sufficient to achieve the targeted tidal volume. (From Ref. 57.)

### B. A Strategy for Weaning Patients with Airflow Obstruction from Ventilatory Support

Taking into consideration the advantages and shortcomings of the techniques described above, as well as the complex underlying physiology of severe airflow obstruction, a defensible strategy for attempting machine withdrawal would emphasize the following key elements:

1. Reverse the underlying process that led to the acute worsening. Several days of nearly complete ventilatory rest may be required initially. Attention to cardiovascular, fluid, electrolyte, nutrition, comfort, and mental status are crucial. Positional effects, air swallowing, gastric distension, cough fractures, muscle strain, and constipation are frequently overlooked reasons for discomfort and agitation.

2. Do not stress the patient beyond the point of incipient fatigue or obvious dyspnea. Chaotic breathing rhythms, vigorous use of the accessory muscles of breathing, diaphoresis, an elevated frequency–to–tidal volume ratio, and irregular or discoordinate breathing (paradox, alternans) must be avoided.

3. Assure adequate sleep. This often requires an increased nocturnal level of ventilatory support (AMV, high-level SIMV, or increased PSV). A mild and rapidly eliminated sedative or hypnotic may be helpful in some instances.

4. Maintain effective bronchodilation, secretion clearance, and infection control throughout the weaning period, both before and *after* extubation has been accomplished.

5. Minimize the use of corticosteroids and paralytic agents in the full support phase that precedes the weaning period. The daily equivalent of 40–60 mg prednisone in the acute period (first 2–3 days) is generally adequate for optimal benefit. Higher doses tend to disrupt sleep, cause mental confusion, disturb electrolyte balance and produce muscle weakness. The steroid dose should be tapered quickly after obvious progress has been made.

6. For all intubated patients who draw spontaneous breaths during CPAP or SIMV, endotracheal tube resistance must be offset with a level of pressure support commensurate with tube diameter and minute ventilation ($\approx$4–7 $cmH_2O$). Pressure support should be withdrawn entirely before extubation in patients who are at risk for postextubation upper airway edema (e.g., women, patients with large neck diameter and those with a previous history of need for reintubation).

7. In general, patients with severe airflow obstruction, neuromuscular weakness, or cardiac dysfunction do not easily tolerate abrupt transitions from full support to spontaneous breathing. Therefore, machine power should be withdrawn very gradually, with the rate of withdrawal guided by patient tolerance. This is especially important in the first phase of PSV withdrawal. The ability of the patient to resume responsibility for breathing should be frequently retested, as this can change with surprising suddenness, even after a rather lengthy period of ventilatory support.

8. The method of gradually reducing machine power (SIMV or PSV) must be individualized. Attention is paid to overcoming tube and circuit resistance, maintaining adequate end-expiratory lung volume, and periodically giving one or more "sigh" breaths to help prevent atelectasis during monotonous shallow breathing. When SIMV is used as the power source, CPAP and PSV are also employed at low levels to offset tube resistance and auto-PEEP, as well as to confer flexibility; when PSV is used as a power source, a few large (≈10–12 ml/kg), volume-controlled breaths are provided each minute to help maintain recruitment (Fig. 10). Decrements in machine support are made with due respect for the relative weakness of the patient in relation to the workload and the understanding that SIMV tends to reload the patient earlier than PSV. When PSV is used, an empirical 3- to 5-minute mini-trial of the intended change under direct observation often proves invaluable, especially when there is demonstrated minute-to-minute instability or trendlike deterioration of the monitored parameters. During this brief assessment period, the tidal volume, frequency and the $f$:$V_T$ ratio may provide guidance, quickly demonstrating the likely tolerance or intolerance to an intended setting adjustment (33). Heart rate and clinical signs of comfort or distress help to define the appropriate level of support.

9. The patient must be continually reassessed with respect to the suitability for a weaning attempt. Marked changes may occur quickly in these patients, especially if a good night's sleep or a noticeable reduction in the $\dot{V}_E$ has occurred between points of evaluation. Muscular coordination, for example, frequency improves over very brief intervals. For some patients, maintaining a specific posture may be essential to optimizing muscle strength and efficiency. For patients with severe COPD, this is often the chair-sitting position, one in which the patient is able to use his or her arms to brace the accessory muscles for optimal muscle action.

10. Because many patients experience an increase of upper airway resistance postextubation, and because reloading of respiratory system may be deferred until very low levels of PSV are used, caution should be applied in making the decision to extubate. PSV should be tapered to low levels before this is undertaken. Postextubation, there should be special care directed toward maintaining secretion clearance, effective oxygenation, appropriate cardiovascular support, and adequate sleep. Noninvasive ventilation may occasionally be helpful in overcoming postextubation dyspnea. Although it is important to provide an adequate number of calories, oral feedings are hazardous in the first few hours to days postextubation; swallowing must carefully tested in order to avoid aspiration.

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# 30

# Management of the Chronic Obstructive Pulmonary Disease Patient Ventilated for Acute Respiratory Failure

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Seminal to the management of patients requiring the physiological support of the intensive care unit (ICU) is the achievement of a specific and accurate diagnosis. The institution of specific therapy then follows. The management of physiological support to sustain life until specific therapy is effective without threatening the patient's well-being is the essence of the ICU. The prevention of morbidity from the ICU environment, though last to be considered, often determines the patient's outcome. The ICU physician therefore devotes scrupulous attention to the prevention and identification of ICU-associated morbidity, which is the thrust of this chapter. Related topics, such as the importance of diagnosis and management of the underlying disorders causing acute respiratory failure (ARF) in chronic obstructive pulmonary disease (COPD), have been dealt with in Chapters 11 through 16. The importance of specific therapy is addressed in Chapters 18 and 19. The essentials of non-ICU treatment are dealt with in Chapters 22 through 26. Chapters 27 through 29 present a critical appraisal of mechanical ventilation and its refinements.

It has been said that very little medical practice is based on fact and the rest is based on opinion. In intensive care this is especially true. Most forms of physiological support and monitoring strategies are based on the belief that measurement and improvement of a physiological parameter has a beneficial

effect on outcome. New strategies are introduced to supplant old ones with neither having been subjected to proper evaluation. It is uncommon for ICU treatment to be subjected to large randomized trials that measure outcome (Level I evidence). Most of the issues we are about to review are based on Level II evidence (small randomized trials with uncertain results), Level III evidence (small nonrandomized trials with contemporaneous controls), Level IV evidence (nonrandomized trials with historical controls), or most commonly, Level V evidence (uncontrolled case series) (1).

## I. Airway Management

Stable secure access to the airway is essential for ventilator management. In current practice this means either an endotracheal tube (ETT) or a tracheostomy (TT). More recently, the availability of noninvasive mechanical support using nasal masks or mouthpieces and special proportional assist ventilators are showing promise. These techniques remain investigational, however, until other techniques evolve. The major issue to be decided is which type of airway to use, an ETT or TT (2,3).

### A. Endotracheal Tube

The endotracheal tube in current use is made of silastic, with a low-pressure, high-volume cuff. It provides a stable, secure, reasonably low-morbidity airway for the majority of patients who require short-term ventilation. The primary disadvantage of an endotracheal tube is the potential for a laryngeal injury (4). Patients at increased risk of endotracheal tube–induced morbidity are identifiable by risk factors, many of which are related to abrasion from excess mobility of the tube. This is made worse by irritable fighting or "bucking" patients, a tube too large in size for the larynx, positioning with the cuff too high in the cervical trachea, and duration of intubation (2). The identification of the nature and location of this morbidity has been known for 15 years (4–9), but the exact pathogenesis is not clear. Injury related to the duration of intubation includes ulceration of the vocal cords very frequently, posterior commissure stenosis occasionally, tracheal ulceration or bleeding occasionally, and tracheoesophageal fistula rarely. Problems associated with the procedure of intubation itself include intubation of the esophagus, pneumothorax, upper arterial damage, or dislocation of the arytenoids.

### B. Tracheostomy

Tracheostomy, on the other hand, is not associated with any laryngeal injury. There is, however, a small but definite incidence of operative morbidity (10), including perioperative bleeding and pneumothorax. Late sequelae include tracheal ulceration, which is quite common. Tracheoesophageal fistula and innomi-

nate artery fistula are fortunately rare. The replacement of a dislodged tracheostomy tube in a freshly fashioned stoma can lead to a false passage. The incidence of nosocomial infection is higher with tracheostomy.

### C. Airway Selection

Despite the use of tracheostomy for 3000 years, there is still no clear-cut agreement regarding the ideal timing for the procedure in the ventilated patient (2). Table 1 outlines the pros and cons of ETT and TT. The identification of morbidity from ETT was outlined very carefully in a prospective study of 200 patients by Whited (4). It is clear that the morbidity of laryngeal injury associated with endotracheal intubation rises to unacceptable levels 7–11 days after intubation. Nonetheless, many factors must be taken into account when making the decision to perform tracheostomy if the patient has an ETT in place. If the patient has been intubated for 7 days and shows no clear evidence of being easily weaned within the next day or two, the patient should probably undergo tracheostomy. On the other hand, if the patient is physiologically unstable, has a coagulopathy, or has other, more pressing problems to be dealt with, tracheostomy may be deferred on the judgment of the attending physician (3). A restless, gagging patient who has poor oral hygiene and secretions that are difficult to control would, in the judg-

**Table 1** Comparison of Endotracheal Intubation and Tracheostomy

| Characteristic | Endotracheal tube | Tracheostomy tube |
|---|---|---|
| Stability | Moderate | Good |
| Security | Inadvertent extubation—10% | Inadvertent extubation rare, but dangerous before 5 days |
| Patient mobility | Limited | Good |
| Ease of care | Awkward | Easy |
| Control of secretions | Difficult | Easy |
| Comfort | Uncomfortable | More comfortable |
| Communication | Poor | Acceptable |
| Nutrition | Cannot swallow | Oral feeds possible |
| Morbidity | | |
| Early | Arytenoid injury | Operative bleeding |
| | Esophageal intubation | Pneumothorax |
| | Right mainstem intubation | |
| Late | Dysphonia | Tracheal stenosis |
| | Cord immobility: aspiration | Increased risk of infection |
| | Subglottic stenosis | Erosion innominate artery |
| | Lip, facial irritation from fixating tape | |

ment of most physicians, require a tracheostomy earlier than at 7 days (2). In addition, patients suffering from disorders identified at the outset as needing airway management for an extended period of time would also require early tracheostomy. Anecdotal evidence suggests that the following patients are at special risk for developing postextubation laryngeal complications: female patients or patients with conditions such as diabetes mellitus, purulent pneumonias, rheumatoid arthritis, ankylosing spondylitis, or a tendency to keloid formation (2). In addition, if laryngeal trauma is expected, either before or during intubation, early tracheostomy may allow specific diagnosis and early treatment (Table 1).

### D. Cricothyrotomy

As an alternative to tracheostomy, cricothyrotomy has been recommended and performed in a limited number of institutions for many years. The ease of access to the airway makes it ideal for inexperienced operators, and large consecutive case studies show morbidity as low as tracheostomy with approximately the same incidence of long-term airway complications. Though not in general use as an elective procedure, it is certainly a viable alternative (13,14).

## II. Ventilator-Associated Pneumonia

The insertion of an airway to allow mechanical ventilation of chronically ill patients with ARF immediately compromises all of their defense mechanisms against infection. Effective cough is precluded, mucociliary clearance impeded, bronchospasm worsened, airway resistance increased, and likelihood of colonization with multiresistant hospital organisms increased (16). It is not surprising, therefore, that the major problem in these patients is the diagnosis (15) and effective management of ventilator-associated pneumonia (VAP). This important complication is discussed in detail in Chapter 12. Suffice it to say, there is an emerging consensus on the approach to diagnosis of VAP (17). The issue becomes important if the patient has a clinical suspicion of pneumonia described as (1) radiographic appearance of a new or progressive pulmonary infiltrate, (2) fever, (3) leukocytosis, or (4) purulent tracheobronchial secretions. These clinical criteria define patients with a clinical suspicion of VAP, who require further testing (17). For these patients it is necessary to obtain lower respiratory tract secretions to confirm the diagnosis of a definite pneumonia.

Our emerging understanding makes clear the need for definitive sampling of lower respiratory tract secretions, with protected brush specimen (PBS) or a bronchial alveolar lavage (BAL) before the institution of antibiotic therapy (18). The interpretation of these specimens from patients who are receiving antibiotic therapy is still controversial, making pretreatment testing important (19,20). Clinical judgment alone is frequently inadequate to make therapeutic choices (18).

Most disturbing is the observation that patients on antibiotic therapy deemed appropriate based on cultures obtained have a very high in-hospital mortality, approaching the mortality of patients on antibiotic therapy considered inappropriate (18).

## III. Stress Ulcer Prophylaxis and the Risks of Bleeding and Infection

The importance of an integrated comprehensive approach to the management of COPD patients with ARF is very apparent in the emerging understanding of the relationship between the risk of overt stress-related gastrointestinal bleeding, prophylaxis of stress-related bleeding, and the risk of nosocomial pneumonia. Up until the early 1980s, the incidence of clinically significant stress-related upper GI bleeding in intensive care patients was high—approximately 12%. Because of this, prophylaxis with measures designed to control gastric pH became standard practice, which may explain the reduction of clinically important bleeding to between 0.7 and 2% in current ICU practice (21–23). It is entirely possible, however, that better ventilator care, improved diagnosis, and management of sepsis and a better understanding of availability and importance of nutrition have caused the decreased incidence of bleeding quite independent of prophylaxis (21). Though widely practiced, prophylaxis carries with it both an associated financial cost and an increased risk of pneumonia. This is due to bacterial colonization of upper GI tracts of patients with high gastric pH. Two prospective studies have shown prophylaxis using histamine 2 receptor antagonist (with or without antacid) (24) and increased gastric pH (25) to be predictors for ventilator-associated pneumonia. However, meta-analysis looking at the eight randomized controlled trials of stress ulcer prophylaxis and nosocomial pneumonia suggested a risk reduction for ventilator-associated pneumonia with the use of stress ulcer prophylaxis (26). Poor methodology, small sample sizes, and use of more than one therapy have made a large prospective randomized trial necessary to review these findings. Such a trial is presently being conducted.

In the interim, clinicians must use the best information available in order to adopt a plan. They must balance the need for stress ulcer prophylaxis to prevent clinically significant bleeding in their ventilated COPD patients with the possible increased risk of pneumonia. The independent risk factors for bleeding include presence of a coagulopathy or a predicted need for ventilation beyond 48 hours (22,23). These guidelines are useful in making a decision about prophylaxis in a subgroup of patients.

If the patient can be fed, prophylaxis may not be necessary. The need for early feeding of COPD patients with ARF is self-evident. Many of these patients suffer from malnutrition and respiratory muscle dysfunction, which improves

subsequent to refeeding. This must be done carefully to avoid hypercarbia from heavy carbohydrate loads (27). The need for nasogastric tubes to sustain enteral feeds in these patients also predisposes them to aspiration and the risk of nosocomial pneumonia. Nasogastric tube feeds may elevate the intragastric pH and create additional risk factors for colonization. Many of these patients have a generalized decrease in GI motility (28). This is exacerbated by the fact that many of them receive narcotics and/or sedative drugs while in the ICU. The importance of nutrition in COPD patients with ARF and recommended techniques for nutrition are outlined in Chapter 19. Our recommendations are as follows:

1. Offer stress ulcer prophylaxis only to patients who have a coagulopathy or will need ventilation well beyond 48 hours.
2. Do not administer stress ulcer prophylaxis to patients who can be fed enterally.
3. Use the smallest feeding tube practical for enteral feeds.
4. Avoid use of drugs that decrease GI motility.

## IV. Analgesia/Sedation

We have a natural desire to provide comfort to the irritated, coughing, tired, and restless patient with COPD and ARF. This must be tempered by the necessity for creating a treatment plan on the day of admission that is directed to promoting independence of the patient. Since most patients with COPD and ARF are not suffering from conditions associated with severe pain, only moderate amounts of analgesics are usually required to provide a satisfactory tolerance for endotracheal tube and ventilator synchrony. Anxiety, which is manifested by agitation and restlessness, may be treated with titrated doses of an anxiolytic, usually a benzodiazepine. If the patient is in a confused, agitated state or a delirium and does not respond to the above measures, and metabolic derangements have been excluded or treated, the addition of a major tranquilizer may be necessary. Some general guidelines that may be useful include the following:

1. Some narcotics and tranquilizers may cost 10 times more than others (29). Though minor pharmacological and physiological differences exist, no outcome studies exist that show differences in results in morbidity or mortality.
2. A drug with an extremely short half-life should only be used if long-term effects are not desired or needed.
3. Titration of small doses with frequent reassessment is essential.
4. Analgesia and/or sedation should be used in such a way as to promote rather than impede patient independence and involvement in his or her own care.

For patients whose gas exchange remains poor with high $FiO_2$, who have high peak airway pressures, and for whom achieving adequate patient-ventilator synchrony is not possible, paralysis with neuromuscular blocking agents should be considered (30). The physician must be alert to the risk of long-term myopathy in patients treated with neuromuscular blockers and large doses of corticosteroids (31). For patients with intractable airway obstruction for whom sedation is essential, Propofol has been shown to have a bronchodilating effect (32).

## V. Pneumothorax

Surprisingly little data exist in the form of prospective series regarding the incidence of pneumothorax in patients with COPD and ARF who are ventilator dependent (33). This notwithstanding, common experience would indicate that the incidence is significant. The combination of multiple bullae, overdistended lungs, auto-PEEP, and gas trapping exacerbated by positive pressure ventilation all conspire to put the patient at risk. In addition, a very significant incidence of pneumothorax is created by ICU procedures, including internal jugular vein catheterization, subclavian vein catheterization, and thoracocentesis. The occurrence of pneumothorax in mechanically ventilated patients is very significant. The potential for the creation of tension pneumothorax is higher than in spontaneously ventilating patients, and if it occurs, it may lead to circulatory collapse and death within 2–3 minutes. It should be suspected in any ventilated patient whose condition deteriorates unexpectedly who displays evidence of increased intrathoracic pressure with elevated neck veins, pulsus paradoxus, suffusion of the head and neck, and elevated ventilator airway pressures. This may be associated with rapid hemodynamic compromise. A clinical examination of the patient and a quick check for airway placement or ball-valve tube obstruction should be done. The clinical detection of pneumothorax is exceedingly difficult. The physical signs may not be easily discernible. If time permits, confirmation of the diagnosis with a portable chest radiograph is advisable. If not, emergency chest tube placement, in the second intercostal space anteriorly or the fifth intercostal space in the mid axillary line, is warranted (34). If localizing signs in the chest are present, the silent enlarged resonant immobile hemothorax should receive the chest tube first. If tube placement is satisfactory and a clinical response does not ensue in seconds, a chest tube should be placed on the other side as well, which may be slow to close.

If the patient suspected of pneumothorax is ventilating spontaneously and deteriorating rapidly and the clinician has the choice of endotracheal intubation or chest tube placement when the clinical diagnosis is suspected pneumothorax, the chest tube should be placed first. Spontaneously breathing patients with degrees of tension pneumothorax may maintain adequate circulatory function, even though they develop progressive $CO_2$ retention. Intubation and mechanical ventilation

decrease venous return dramatically in these patients. The cessation of spontaneous respiratory efforts and circulatory collapse follow much more quickly.

## VI. Bronchopleural Fistula

Emphysematous blebs may rupture or the placement of a chest tube may inadvertently enter a bleb and be associated post pneumothorax with a large bronchopleural fistula. This problem in a COPD patient can be a difficult challenge to clinical judgment. The risks of operative intervention are high in marginal patients, and the results are unpredictable. Surgery to close the bleb or a thoracostomy designed to prevent recurrence may be associated with other prolonged air leaks. Conventional wisdom would indicate that time, patience, and adequate drainage with numerous thoracostomy tubes, if needed, will ultimately result in closure of fistulas in these patients (35).

## VII. Metabolic Derangements

### A. Potassium

Many factors conspire to create fluctuations in serum potassium during the early hours of mechanical ventilation of COPD patients with ARF. The use of corticosteroids, theophylline, and beta-agonists promote potassium shift in and out of cells and may promote quite dramatic changes in serum potassium. The use of diuretics may also conspire to create hypokalemia and rapid shifts in serum potassium. These changes may be expected, but their magnitude cannot be predicted. Therefore, initial and subsequent measurements of serum potassium are essential until the patient is stabilized. It is preferable to plan in 24-hour segments for potassium administration than to respond with large intravenous doses over a short period of time. If chronic, significantly low serum potassium levels ($<3.5$) reflect a deficit of potassium in the order of 300–400 mEq of potassium in the average adult. Replacement should be planned over a period of 2–3 days.

### B. Phosphate

Hypophosphatemia is a well-recognized metabolic complication of the ventilator management of ARF in COPD patients (36,37). Risk factors known to be associated with hypophosphatemia include:

1. Rapid correction of respiratory acidosis by mechanical ventilation
2. Glucose administration in previously poorly nourished patients
3. Initiation of parenteral nutrition
4. Use of antacids
5. Corticosteroid, diuretics, theophylline, and beta agonist drugs

The exact mechanism of hypophosphatemia in these patients is not known. Risk factors associated with it may be causal or merely coincidental. It is clear, however, that the correction of hypophosphatemia by phosphate infusion improves diaphragmatic function dramatically and avoids the other serious complications of hypophosphatemia, including ventilatory failure, an increase in oxyhemoglobin affinity, hemolytic anemia, rhabdomyolysis, and metabolic encephalopathy. Prophylactic phosphate replacement is not indicated. Measurement of phosphate at 12 and 24 hours should be performed when COPD patients undergo mechanical ventilation.

## VIII. Thromboembolic Disease

Pulmonary thromboembolism as a precipitating factor of ARF in COPD has remained a diagnostic dilemma. The exact incidence is not known, but estimates vary from 9 to 20%. The initial investigation and management of thromboembolism as a precipitating factor of ARF in COPD is discussed in Chapter 14.

Once the patient arrives in the ICU, many factors predispose to venostasis, thrombosis, and thromboembolism. They include immobilization, frequent cannulation of large veins, and changes in platelet function. Because of its proven efficacy in similar disorders and low risk in the absence of coagulation abnormality, prophylactic subcutaneous heparinization is recommended and commonly practiced in this group of patients. Good outcome studies evaluating subcutaneous heparin in this particular population are not available.

## IX. The Decision to Ventilate and Resuscitate

Physician estimates of patient survival are quite variable (38,39). They depend on the discipline of the physician and the data used in the decision making. Though life tables exist for some common conditions, very little hard data are available to aid in predictions of survival for patients with complex illnesses. This leads to difficulty when deciding whether to offer mechanical ventilation to patients who have severe COPD with ARF for whom weaning may be difficult or impossible. No prospective randomized trials exist to aid in evaluating the pros and cons of offering mechanical ventilation in this setting. Acuity scoring systems such as APACHE II and III are useful for population analysis but cannot be applied to individual patients. Although chronological age is independently associated with in-hospital mortality for patients with chronic lung disease, other variables are much more important so that age alone cannot be used to predict the appropriateness of mechanical ventilation (40). For those who are offered mechanical ventilation, however, and go on to require cardiopulmonary resuscitation, emerging data are helpful to physicians attempting to decide what course to follow (41). Cardiopulmonary resuscitation (CPR) was developed for the management of patients

with acute cardiac events. It is primarily physiological support for a patient dying from a rhythm disorder with a specific algorithm for management of rhythm disorders. It is becoming clear that patients who present in medical and surgical ICUs with acute illnesses superimposed on chronic underlying conditions who require CPR rarely survive to hospital discharge. This is not surprising when one considers that most of these patients suffer from multisystem organ failure. Our inability to clearly predict 6- or 12-month survival for COPD patients with ARF indicates a trial of ventilator therapy. The poor outcome for CPR in this setting, however, indicates that it is probably not indicated for those who fail the therapy.

In summary, ventilator management for patients suffering from COPD is based on the premise that a short term of physiological support, with mechanical ventilation, will buy time until the clear diagnosis of and specific therapy for the precipitating factors or cause of the exacerbation have had time to be effective. Since the cause of death in these patients is often associated with morbidity acquired in the hospital rather than with the primary disease or precipitating factor, the most important role of the astute clinician is in the prevention of the complications.

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# 31

# Future Developments for Imaging in Special Care Units

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## I. Introduction

The proliferation of special care units (SCUs) over the past 20 years has been in response to major shifts in medical care. Contributing to the increase in SCU patients are an aging population, societal commitments to maintain patients on life-support systems for weeks or months, and the increase in complex surgical procedures, even in debilitated or older individuals. In many institutions, SCUs have been separated into medical, surgical (usually postoperative), and cardiac units.

Imaging is common to all of these specialty units, and no distinction will be made among them. In hospitalized patients, a high percentage of chest radiographic examinations are performed as portable examinations. In large tertiary care medical centers, the percentage of chest radiographs obtained at the patient's bed may reach 50 or 60% (1). Often more than two thirds of these are obtained within special care units.

Other imaging modalities that can be transported to and used within an SCU include ultrasound and portable fluoroscopy. Computed tomography (CT) examinations are increasingly performed on SCU patients, even though these critically ill individuals may have to be moved some distance to a CT scanner in a radiology

department. Magnetic resonance imaging (MRI) has experienced much less application to the SCU patient, because of the configuration of the equipment presently available and the difficulty with using iron-containing medical hardware in proximity to high-strength magnetic fields.

In this chapter, we will deal with several aspects of imaging in an SCU: conventional radiography and improvements being made in this area, fluoroscopy, digital chest imaging, CT and MRI and their applicability to individuals within an SCU, and portable ultrasound examinations. The conclusion of this chapter will suggest types of equipment that should be considered in planning efficient utilization of imaging technology in an SCU.

## II. Conventional Radiography

Bedside radiography in an SCU has become completely integrated into patient care and is as indispensable as the physical examination of the patient. Radiographs are obtained on a periodic basis to monitor patient progress, following most interventions such as the insertion of tubes and catheters into the patient, and most commonly following a change in the patient's clinical status. The utility of this type of patient monitoring has been well substantiated in several excellent studies (2–4). In approximately 40% of instances, significant information is provided that will impact on patient care. According to one study (5), 50% of nonroutine portable chest radiographs resulted in a change of therapy or of diagnostic considerations.

The methods by which portable chest radiographs are obtained has changed minimally in the last two decades and, in many instances, have not incorporated the available newer technologies. For most portable radiographs, a conventional film screen combination is used without a grid to reduce scattered radiation and without an inclinometer or other device for determining patient position. In most circumstances, the distance from tube focal spot to the film is varied and unknown, producing variable magnification of the intrathoracic structures such as the heart. At present, 10–15% of portable chest radiographs obtained in an SCU are suboptimal (1). The factors limiting the quality of this examination are mainly related to limitations inherent in the portable radiographic equipment and to inadequate instruction for technologists. Degradation of the chest image is from breathing motion, patient rotation, poor patient position, variability in the technical factors used, and the relatively low kilovoltage of the x-ray beam provided by portable generators.

An optimal portable chest radiograph can accurately depict large abnormalities as well as the fine details of structures within the lungs such as small vessels and lobular partitions. The denser portions of the image, as in the retrocardiac and retrodiaphragmatic regions, must be visualized on the same image as the

lungs. Overlying bony and soft tissue structures inhibit visibility of lung detail and should be rendered less apparent on an optimal chest radiograph. Any inserted tubes or catheters must be clearly depicted in relation to their surrounding anatomical structures. It is also important to achieve consistency in the appearance of the thorax on sequential images obtained at intervals or hours, days, or weeks. This requires a concern for detail in obtaining and processing of the chest radiograph. In fact, poor film processing, especially when exhausted developer has been used, is a major cause of image degradation.

Technologists who are inexperienced or poorly trained will not be able to time the x-ray exposure to the respirator so that the chest radiograph coincides with end-inspiration. Chest radiographs obtained at low lung volumes, with or without underexposure, can simulate the presence of significant air space consolidation at the lung bases or findings suggesting left heart failure and pulmonary edema.

Poor patient positioning with rotation of the patient or patients positioned in a lordotic or kyphotic relationship to the x-ray cassette, as well as the excessive use of supine radiographs—when the patient could reasonably be upright—will decrease the diagnostic information available from portable chest radiographs.

### A. Standardization of Procedures

Immediate improvement in radiographic quality in an SCU can be obtained by standardization of the procedures by which the studies are obtained. These include:

1. A standard x-ray tube:film distance (usually between 48 and 53 inches).
2. Standardization of the peak kilovoltage setting of the x-ray tube (usually 80 kVp). (Changes in film density is then obtained by varying the milli-amperage and time of exposure, referred to as the MaS.)
3. Routine use of upright images whenever possible. Knowledgeable x-ray technologists and cooperative SCU personnel can have a fundamental impact on film quality. Giving dedicated technologists primary responsibility for quality assurance in special care units is an excellent approach.

### B. Film–Screen Combinations and Grids

In general, wide-latitude film–screen combinations should be used in an SCU (6). Even with relatively low voltage examinations, exposures can be achieved that will allow imaging of the lung parenchyma, as well as provide penetration of the mediastinum, heart, and abdomen.

In 1990, the Eastman Kodak Company introduced a new combination of film and intensifying screens specifically for chest radiography. This system,

called "InSight," uses two intensifying screens with different sensitivities, matched to film with different emulsions on either side. Crossover of light between the two sides of the film is prevented with a light-absorbing dye incorporated into the base of the x-ray film. The combination of a low- and high-sensitivity system within one film produces improved imaging of both the lung parenchyma and the higher attenuation areas such as the mediastinum (7). We have had experience with the use of this system in combination with a nonfocused grid developed by Kodak for portable examinations. The system produces considerably better images than are available with standard film–screen combinations.

### C. Scatter Reduction

In conventional chest radiography, up to 40% of the blackening of the radiograph in selected areas will be due to scattered radiation (8,9). Radiation is scattered predominantly from the patient and degrades the quality of the image without providing any information. Reduction in scattered radiation in conventional chest radiography is achieved with focused grids, which eliminate the scattered radiation impinging on the film from an angle other than the x-ray tube. For acceptable reduction in scattered radiation, a 12:1 or better ratio grid is required. With this high ratio, the relationship between x-ray source, grid, and film is critical. Any deformity of the grid or malalignment will produce an excessive attenuation of the x-ray beam, usually asymmetrically across the radiograph. Practical experience indicates that focused high-ratio grids cannot be used for portable examinations. A compromise is therefore reached between the voltage that can be reasonably used and the absence of a scatter-reduction grid technique. The upper limits of technique acceptable without a grid is peak energy for the x-ray beam of 80–90 kV. At this voltage, suppression of the bony structures of the thorax is less than at higher voltage settings, but the results are acceptable in all but the most obese patients. Development of cross-hatched or pinhole grids, which could be light enough to be incorporated into the x-ray cassette and not produce excessive attenuation of the beam when malaligned, awaits further development.

### D. Information Transfer

Fundamental to the imaging of the critically ill patient is that the interpretation of the imaging study be rapidly sent to those members of the health care team involved in decisions regarding the patient. Information transfer can be considered in two separate but interlinked parts: (1) transfer of the interpretation of the study and (2) transfer of the image itself.

#### *Transfer of the Interpretation*

Transfer of the interpretation of radiographs of patients residing in a special unit invariably requires rapid handling of the study. In most situations, the time

between obtaining the image and its interpretation being available should be less than one hour. If this is not possible, methods must be instituted for the images to be made available directly to the SCU personnel for their interpretation.

Communication of the results of chest radiographs and other imaging studies should be formalized and routine. The simplest method is to telephone all results or all positive results to the SCU. Systems are available for a written or dictated report to be instantly available via telephone lines or dedicated fiber optic transmission lines. When the images themselves are sent to the SCU in digital form, the interpretation of the study can be integrated with the image as an annotated image or a contained document.

### *Transfer of Images*

Digital imaging can be achieved in several ways. Common to all these is that at some point the image is in a digital format. Generally, in the field of picture archiving and communications systems (PACS), consideration is given to the method of image acquisition, image transmission and storage, and image display. In Section IV we will deal with image acquisition in a digital format. Here we will discuss images that have been acquired as conventional film–screen radiographs and then digitized. Methods for digitization range from simple to complex (10). The least expensive uses a television camera to access the image, which is usually digitized on a $512 \times 512$ matrix. For chest imaging, this level of resolution is not adequate for interpretation but can be adequate for display in an SCU. For most purposes, laser scanning digitization is preferred. The typical laser system provides a matrix of $2000 \times 2000$ pixels with 1024 shades of gray—generally considered acceptable for diagnosis. The time taken to digitize a $14 \times 17$ inch chest radiograph is 30 seconds or less. Once digitized, the image can be stored, processed with different enhancing algorithms, transmitted, and displayed (Fig. 1). Transmission of the image from the central processing area to the various SCUs is usually achieved with dedicated fiber optic cables.

Once the image is received at the unit, it must be displayed for viewing. Two methods are currently available. The image can be converted back to hard copy, i.e., regenerated as a film-based image (Fig. 2). High-resolution laser printers provide a matrix of $4000 \times 5000$ pixels corresponding to a resolution element of 0.1 mm for a $14 \times 17$ inch radiograph. These printers can also give 4096 shades of gray. The quality of the images is indistinguishable from an original radiograph. The second method of display uses a TV monitor. Most investigators have suggested that a relatively high-resolution system is required, with a matrix of either $1000 \times 1000$ or $2000 \times 2000$ pixels. These systems display images with a fidelity that is definitely sufficient for clinical display purposes and possibly for primary diagnosis.

The limitations of film digitization are largely those inherent in the original image (11). If the original radiograph is too dark or too light, the digital image will

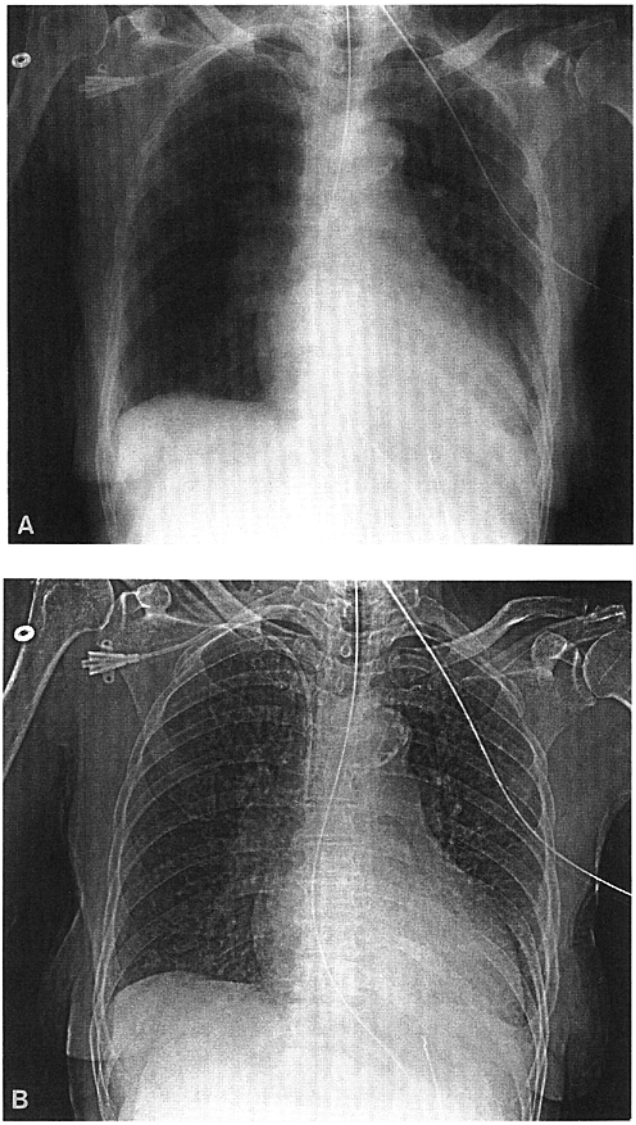


**Figure 1** (A) Digitized image without image manipulation appears similar to a conventional chest radiograph. (B) The same image reconstructed with an edge enhancing algorithm shows the lines and tubes to better effect but produces distortion of the appearances of the lung parenchyma.

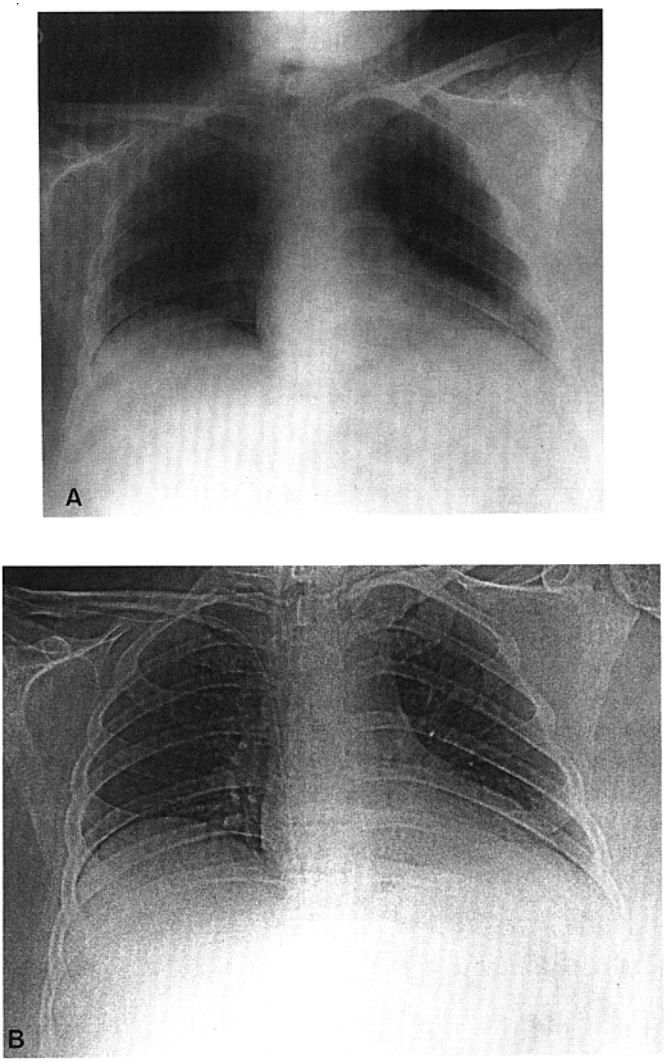


**Figure 2** (A) Digitized chest radiograph without image manipulation in an obese patient does not allow for image of the lung parenchyma and mediastinum on the same image. (B) Edge enhancement of the image improves the density balance but distorts the lung parenchyma.

not compensate, unless special density correction software is incorporated into the system. The cost of digitalization of a film, its transmission, and then printing of a second hard copy film is extremely expensive. This method is thus impractical unless an overriding factor is present, such as the images having to be interpreted at a great distance from their acquisition. Another potential problem is when some images are digital and being viewed on a monitor, while comparison images are conventional radiographs. It is difficult to compare images in different formats.

Video images presently are limited when used for diagnostic purposes. Such images are often less bright than images on a conventional radiographic view box. Viewing conditions therefore must be optimal, and the potential for eye fatigue is present. Unless a $2000 \times 2000$ line monitor is used, subtle findings, such as those found with a small pneumothorax or interstitial edema, may not be detected. One problem that has not received much attention is the difficulty of detecting changes in the caliber of relatively small vessels when they are viewed on smaller images.

## III. Fluoroscopy

Several procedures performed on patients in SCUs are best performed with fluoroscopic guidance if it is convenient and readily available. The routine use of fluoroscopy for insertion of transvenous temporary pacemakers is an example. Insertion of intravascular catheter lines, aortic counterpulse balloon pumps, Swan-Ganz catheters, and endoscopic procedures could all be better performed with fluoroscopic assistance.

At present, portable fluoroscopic units are cumbersome and time consuming to bring to the patient's bedside. Taking the patient to a fluoroscopic suite is often tedious and difficult. Dedicated portable fluoroscopic units within an SCU or a dedicated fluoroscopic suite immediately adjacent to a group of SCUs can be beneficial.

## IV. Digital Imaging

The acquisition, display, transmission, and storage of x-ray images in digital form can alleviate many of the problems with imaging in SCUs. Digital format signifies that the image consists solely of integer numbers, where each number represents a finite area of the image, termed a pixel (the picture element in a digital image). Pixels are normally square, and a matrix of pixels, e.g., $1024 \times 1024$, makes up the image. The spatial resolution within a digital image is a function of the physical size represented by each pixel. Table 1 shows the pixel size for various image sizes and various matrixes. Note that in doubling the matrix size, say from $1024 \times 1024$ to $2048 \times 2048$, the number of pixels used to represent an image quadruples since the area represented by a pixel is one fourth.

**Table 1** Physical Size of Pixels in Digital Projection Imaging

| | Pixel size (mm) | | |
|---|---|---|---|
| Film size (cm) | 512 | 1024 | 2048 |
| 18 | 0.35 | 0.18 | 0.09 |
| 24 | 0.47 | 0.23 | 0.12 |
| 30 | 0.59 | 0.29 | 0.15 |
| 35 | 0.68 | 0.34 | 0.17 |
| 40 | 0.78 | 0.39 | 0.20 |
| 43 | 0.84 | 0.42 | 0.21 |

When an x-ray image is acquired digitally, the number associated with each pixel—the pixel value—is an integer representing the intensity of the light or luminance within the area represented by that pixel. Integers must be within a certain gray-scale range set by the bit depth of the image, where a bit is a power of 2. Thus, a digital image described as having an "8-bit depth" indicates that each pixel can have a value between 0 and 255 ($2^8 = 256$). In this example, the entire x-ray intensity range striking the digital detector must be represented by only 256 integers, even though the actual intensity range for an adult chest image may exceed a 1000:1. Thus, for most thoracic applications, the digital image should be 8–10 bits deep.

Since the eye is an analog detector, images are not viewed in digital form but are converted into an analog form for viewing. Pixel values are converted to light intensity levels on a cathode ray tube (CRT) screen for "soft copy" display, or optical density levels if a "hard copy" film is the display mode. For soft copy display, the conversion of pixel values to light intensity levels is usually variable and controlled by the viewer through window width and window level controls, as illustrated in Figure 3. An image can be viewed under different window width (Fig. 3A) and window level (Fig. 3B) settings to bring out different features in the image.

The digital format has several advantages over the conventional analog format for thoracic imaging. In the digital format, the image is perfectly preserved. Displaying, transmitting, and storing of digital images does not add noise or degrade the image. Digital images can be sent to and stored at multiple locations simultaneously without the time and expense of making copy films. Identical images can be stored on a computer and viewed in a radiology department and also on a display station within an SCU. Images can be transmitted from one location to another accurately and relatively quickly. Unless dedicated transmission equipment is available, phone lines will slow the transmission of images when using

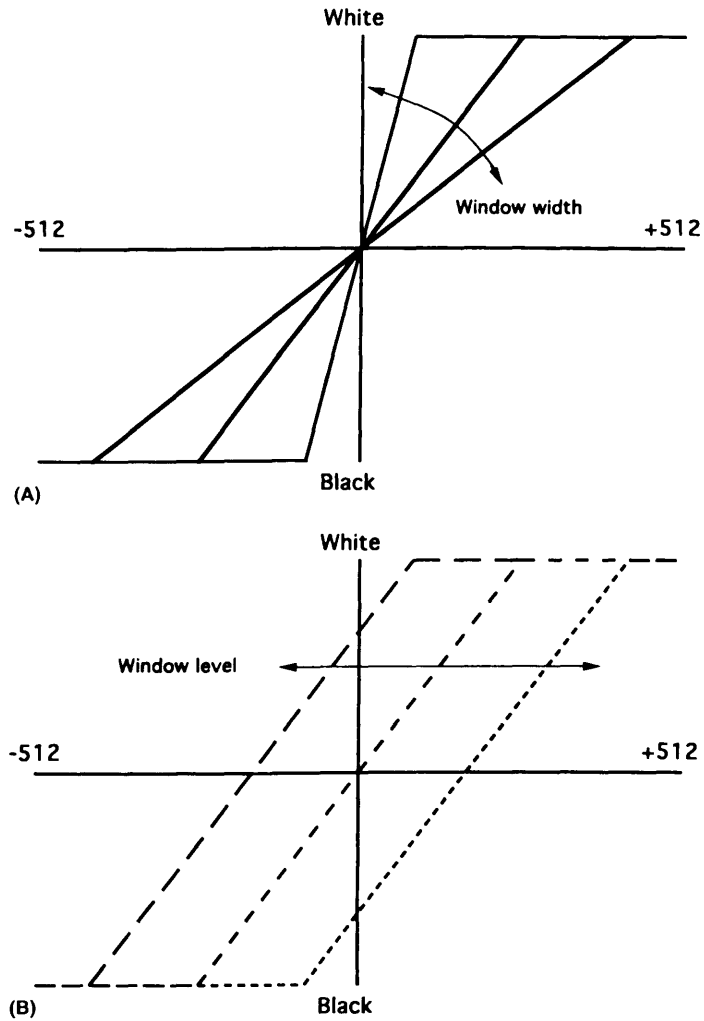


**Figure 3** The relationship between brightness (gray shade) and digital value for an image with 10 bits per pixel. Note that, for all example curves, many values are displayed as black or white. Pixels with these values could not be distinguished from each other. (A) Changing the window level changes the gray shade of the central level digital value, but not the range of values displayed. The analogous control for an analog is system brightness. (B) Changing the window width changes the range of the digital values that are displayed, but not the central level. The analogous control for an analog system is contrast. Window level and width controls are used together to display the desired range (level and width) of digital values in the displayed image. A single image is often viewed several times with different level and width settings.

digital transmission. Digital images can be manipulated by a computer to enhance features and extract precise, quantitative information. For example, the edges of structures can be enhanced, making them easier to see (Fig. 4). Finally and most importantly, digital x-ray detectors can have a greater dynamic range than conventional film–screen recording systems. This feature will be discussed further.

### A. Digital X-Ray Detectors

At present, two methods are commercially available for producing digital images. Conventional film-based radiographs can be digitized, as discussed previously. Digitization can involve either a scanning laser system or a video camera and the signal from the camera captured in digital format. Film digitization is sometimes used for cross-sectional images from CT, ultrasound, or MRI, where the initial image has comparatively low spatial resolution. However, for x-ray imaging, such as in an SCU, film digitization has not become widely available because it is time consuming and the process does not improve upon the quality of the initial radiograph. Digitizing radiographs does not alleviate any of the inherent problems in obtaining a high-quality film within an SCU. One advantage, however, is that the image may be transported over long distances and made available simultaneously at several sites.

The second method for obtaining a digital x-ray image is an x-ray detection system based on photostimulable phosphor (PSP) technology (12–16). This technology was first commercially marketed by Fuji in the early 1980s. The initial system was expensive, requiring an excessively large room for the installation, and did not permit access to the digital data. Consequently, few such systems were installed. However, both the price and size of these systems have decreased, and a digital data port is now available. Several major x-ray equipment manufacturers are marketing the Fuji system under their own logo, while Agfa Gevaert and Kodak have developed their own PSP systems. The result is that the installation and clinical use of PSP systems is increasing rapidly, and the primary application of these systems is in portable imaging (17–20).

PSP imaging, sometimes referred to as computed radiography (CR), works by replacing the film–screen combination of a radiograph with a phosphor plate. These plates are available in the same sizes as standard radiographic films (e.g. 14 × 17 inches). The plate is contained within a light-tight cassette very similar to that used in conventional radiographic imaging. The x-ray exposure is made with the same equipment. The phosphor, a barium fluorohalide ($BaFX:Eu^{+2}$, where X is Br or I), has the property of storing some of the absorbed x-ray energy in the form of an excited crystalline state. Thus, x-ray exposure of the plate creates a pattern of stored energy analogous to the latent image existing within an x-ray film prior to development. The exposed PSP cassette is inserted in a device that removes the plate from the cassette and scans it with a laser beam. The laser beam stimulates

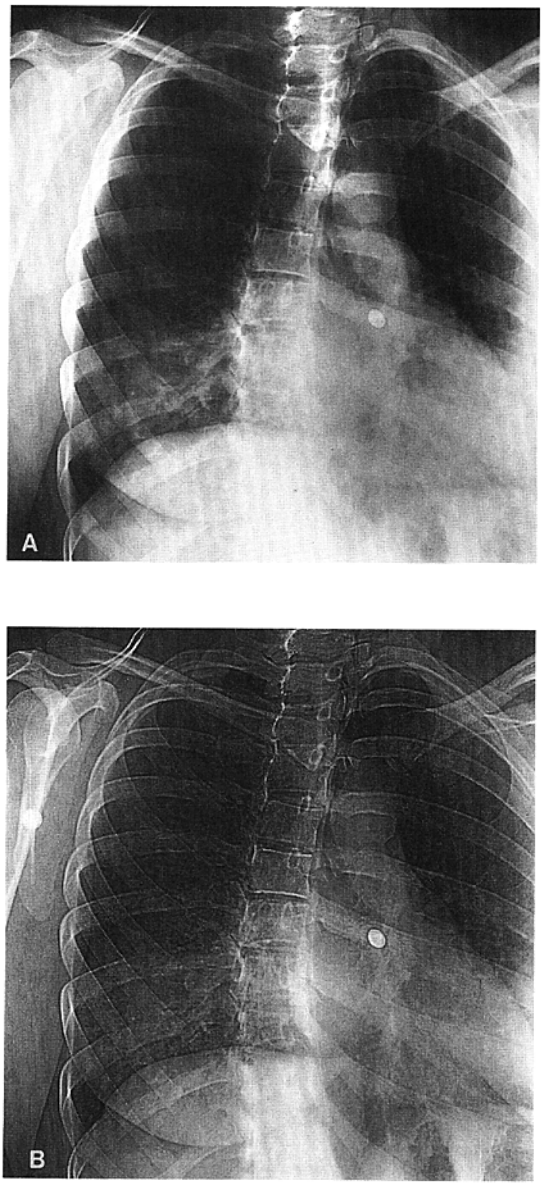


**Figure 4** Effect of edge enhancement. (A) An unenhanced digital adult chest image has been taken with a PSP system. (B) The same image has been digitally processed to sharpen the edges of structures.

the emission of the stored energy from the phosphor in the form of light. Where more x-rays have struck the plate, more light is emitted. The intensity of the emitted light is measured as the laser beam scans the phosphor by digitizing the light signal with a photomultiplier tube. Thus, a digital image is obtained without a film intermediary. The phosphor plate is then exposed to an intense light, releasing any residual stored energy, whereupon the plate can be reused. This overall process is shown in Figure 5.

PSP systems have a significant advantage when compared to an x-ray film–screen system, namely, a much greater dynamic range (15,16,21). In other words, they produce a unique signal in response to a far greater range of x-ray beam intensities. The advantage in portable imaging is that the x-ray exposure factors are far less critical in producing an image. Images are rarely over- or underexposed, as would happen with film if the x-ray beam's intensity was too high or too low. While the quality of the image is affected by the amount of radiation used to form the image, repeat examinations are avoided because over- or underexposure is eliminated.

The quality of PSP images in comparison to film is an important issue that has been studied by numerous investigators (21–26). Image quality is the result of a complex interplay of several factors, including spatial resolution, noise in the image, and sensitivity to contrast differences. Spatial resolution is a measure of the ability of a system to produce a sharp image. In a digital image, spatial resolution is largely a function of the pixel size. For an adult chest image obtained on a $14 \times 17$ inch phosphor plate; the pixel size is $0.2 \times 0.2$ mm. An x-ray film used for chest imaging has an equivalent pixel size of about $0.1 \times 0.1$ mm. Thus, in this comparison, PSP systems have about a factor of 2 lower spatial resolution than film-based radiographs. However, this reduction has not been significant in clinical practice except in a small fraction of cases where subtle detail is important (24–29). It should be noted that some PSP plates of a smaller size, for example, $8 \times 10$ inches, can match the spatial resolution of an average screen–film radiographic system.

Noise is an important factor in image quality and for film-based radiographs is defined as the variation in density from point to point in a uniformly irradiated area. Noise, primarily the result of the randomness of the x-ray absorption process, decreases as x-ray dose increases. In a digital system, the amount of noise is a function of the pixel size and the sensitivity of the detection system. In other words, noise depends on the number of x-rays used to register the pixel value. For a fixed x-ray exposure, when the pixel size is decreased to improve spatial resolution, image noise will increase. As previously mentioned, PSP systems have a large dynamic range for x-rays. However, if a PSP plate is exposed to the same radiation as a film–screen system, the PSP system will be similar or have slightly more noise than the film-based image (26,30).

PSP systems have a bit depth of close to 10 ($2^{10} = 1024$). This value exceeds

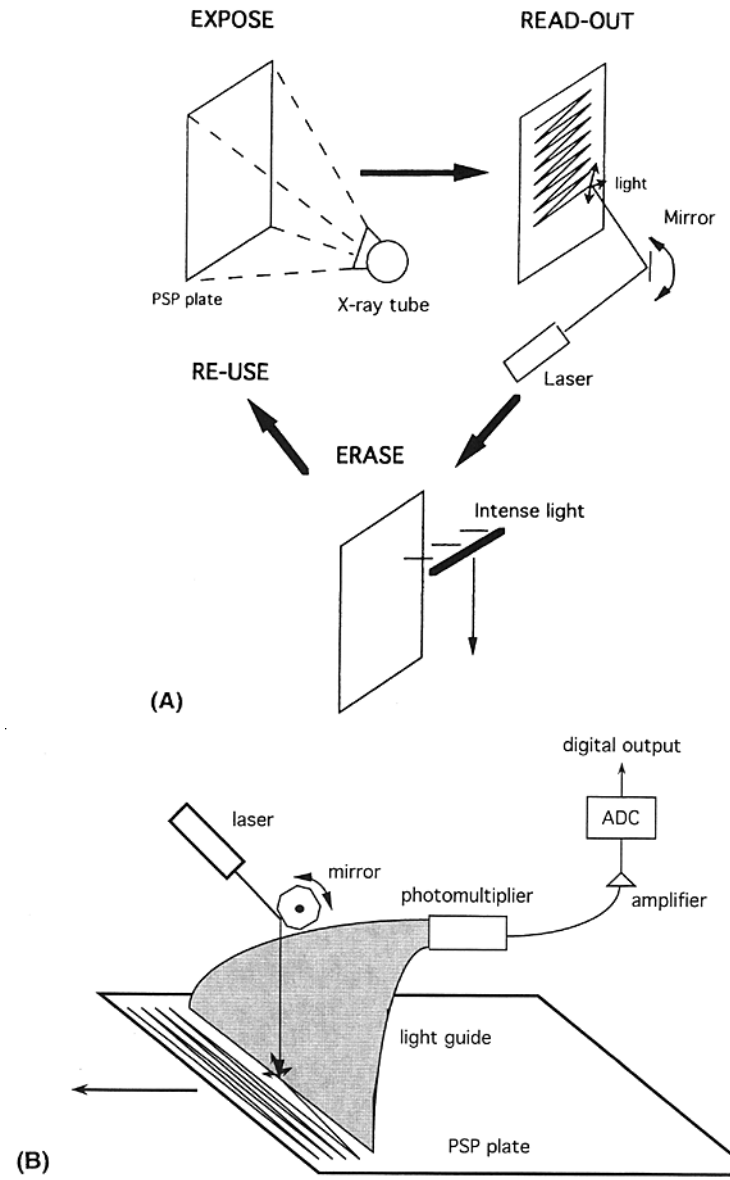


**Figure 5** Re-usable PSP plates. (A) After exposure to x-rays, the plate is inserted in an image reader and scanned with a laser. The plate is then "cleaned" by exposing it to an intense light and is ready for reuse. (B) Within the reader, the plate is moved through a fine, scanning laser beam. A light guide collects the emitted light and channels it to a photomultiplier tube. The signal from this tube is amplified and digitized in an analog-to-digital converter (ADC).

the effective bit depth of film, which is about 8 bits. Thus, PSP systems should perform better than film in capturing the range of x-ray intensities within an image, as illustrated in Figure 6.

Thus, PSP systems have both advantages and disadvantages when compared to film-based radiographic acquisition. In most instances, the slight compromise in image quality is outweighed by the advantage of having a consistent quality image, regardless of the exposure factors, and an image in digital form.

### B. Other Digital Detectors

Although not commercially available, research and development on large-area digital detectors continue. Among the possibilities are charged plate systems (much like a photocopying machine) and various semi-conductor plates (31). However, the requirement that these be compatible with portable x-ray equipment may slow their application. Nevertheless, technologies competitive with PSP systems can be expected to be available within 5 years.

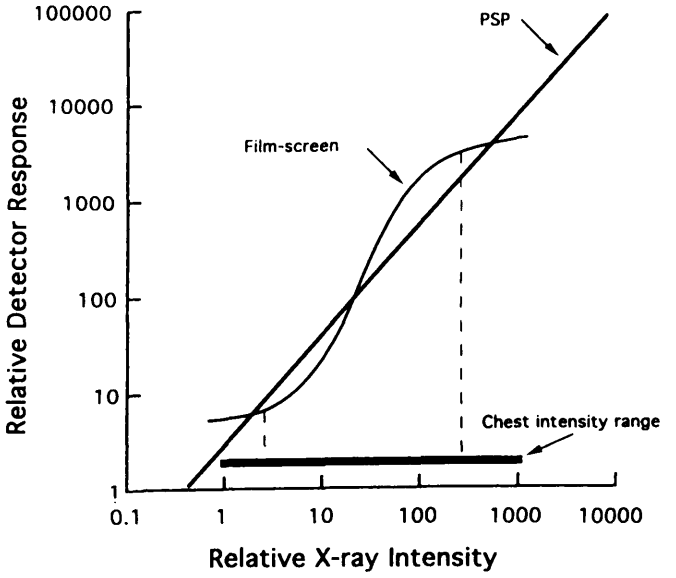


**Figure 6** The dynamic range of a PSP plate compared with radiographic film. The PSP plate can respond uniquely to a range of x-ray intensities exceeding $10^5$, while the latitude of film is less than $10^3$. For an adult chest radiograph, the range of x-ray intensities can exceed $10^3$.

### C. Display Systems

An important rationale for the introduction of digital systems into SCUs is that electronic display stations within or near an SCU can furnish rapid access to CRT images. Several manufacturers now sell these display systems independently or in combination with a PSP unit. A typical arrangement would be a PSP reader unit located in a radiology department, with images sent out over a digital network by a computer server to one or more display stations located in the various units. The display stations themselves usually have enough digital storage for hundreds of images. The optimum configuration is to have digital storage for all active images on all patients within the SCU. Most display stations have two monitors, allowing at least two images to be viewed simultaneously. A computer is used to recall and display the images, usually with simple interactions using a key pad of tracking ball.

The display of PSP images, however, is not trivial. For a $14 \times 17$ inch field size, PSP images will have a pixel matrix of $1760 \times 2140$. Standard CRT monitors cannot display this many pixels. For example, high-resolution video monitors used to display fluoroscopic images in radiology have about 1000 lines, meaning they can display only one quarter of a PSP image at its full resolution. Two thousand–line monitors can display the entire PSP image, but these units cost about $15,000 per monitor and have limited brightness for viewing in a well-lit room. While some display systems do use 2000-line monitors, most have 1000-line displays. PSP images are then displayed at reduced resolution, allowing the viewer to magnify a portion of the image and view this portion at full resolution. Usually, the magnified area can be scrolled around the image using a control switch or tracking ball. While full-screen display of PSP images on 1000-line monitors results in a roughly fourfold loss in spatial resolution compared to film, studies have shown only a slight reduction in diagnostic accuracy (32). Until the cost of 2000-line monitors decreases, 1000-line displays seem to be an appropriate compromise.

A second issue in implementing SCU display systems is the transmission time of images between the PSP reader unit and the display station. Current systems communicate at Ethernet rates, or 1–2 million bits per second (Mbps). While this is a fast rate, a single PSP image contains $1760 \times 2140 \times 10$ bits = 37,664,000 bits. At 1.5 Mbps, ~25 sec are required to transmit one PSP image to the special care unit. This is faster, however, than a clinician walking to the radiology department to view the radiographs or someone taking them to the unit. Transmission times for PSP images are too long to retrieve many images from a central archive of radiology images. This is probably true even if transmission rates for sending and receiving the digital image data were greatly increased, as could be done with fiber optic links and faster hardware. For the foreseeable future, retrieval time for images from an active digital archive will remain too

slow for on-line retrieval to multiple units. Thus, the display station in an SCU must have local storage of the prior images.

### D. Future Developments in Digital Imaging

Recent developments in PSP technology include a remarkable reduction in the size of the image reader. This unit is now small enough to be placed within an SCU. Soft copy image could be available within 90 seconds of the plate being exposed, as the laser reading of the plate would be local. These same images would be transmitted automatically to the radiology department for the radiologist's viewing and interpretation. Better PSP plates will be developed in the near future, with higher spatial resolution. However, display of these images will remain difficult and expensive, as long as a $14 \times 17$ inch image with full resolution is specified. New digital detectors are likely to compete successfully with PSP plates. These detectors will have higher spatial resolution and probably achieve a greater bit depth, for example, 12 bits, compared with the 10 bits for PSP systems. In addition, they may use the incident x-ray beam more efficiently, reducing image noise. The advantage of an increased bit depth is that the image would contain more information about the x-ray signal. X-ray film is configured to present to the eye a range of brightness levels to which the eye is sensitive. The interaction of the x-ray beam and detector may contain a greater range of intensities than can be displayed with film. In chest radiographs, for example, contrast in the lung fields is suppressed in order to prevent overexposure and still obtain information in the underexposed regions of the mediastinum and subdiaphragmatic areas. This compromise is not necessary for digital images with adequate bit depth, as display of the image is separated from its capture and storage. All the information contained within the digital image cannot be seen in a single display. However, the digital image can be displayed with different window widths and level settings to extract all of the information. An example of this is a CT image of the chest. CT images usually have a bit depth of $2^{12}$ (4096 integers). When CT chest images are displayed, one window width and level setting is used for viewing lung structure, a different setting is used for the soft tissues, and a third is often employed for bony structures. The fact that digital images can contain more information than analog images is a powerful driving force behind the increasing use of digital imaging in radiology.

Regardless of the particular detector technology, all future developments will have the common characteristic of being digital. Active images on all patients within an SCU will be available on soft copy display stations nearly instantaneously with their being obtained. These same images will also be available on display systems within the radiology department, and communication between an SCU physician and radiologist will occur electronically. The radiologist will be able to send annotated images to the SCU, with linked reports available for display on the SCU workstation.

The technology now exists for digital images to be sent via a modem over a phone line. Images can be displayed using a PC or Macintosh computer. Thus, it is possible for an SCU physician to have images sent to his or her home or off-site practice. The limitation is that even the best modems today operate at only 19.2 Kbps, thus requiring approximately 32 minutes for transmission for a PSP chest image. This may be practical for highly selected images in some settings, but it is much too long for routine image transmission. Within a few years, however, digital fiber optic cables will be available, replacing the analog cable system now used for commercial television in homes. When this occurs, images could be sent over fiber links at a high speed, increasing the practicality of off-site viewing.

Thus digital technology has improved and will further improve x-ray imaging in an SCU. Images should be of better quality, contain more information, and be available faster than with conventional film–screen imaging.

## V. Computed Tomography and Magnetic Resonance Imaging

In the last 5 years, increased experience with CT and MRI in critically ill patients has highlighted the limitations of conventional chest radiographs for detecting significant intrathoracic disease (33). CT in many circumstances can facilitate earlier diagnosis and obviate the need for more invasive procedures. CT scans of the thorax, abdomen, pelvis, and head are usually obtained to evaluate abnormal findings suspected from conventional radiographs or to evaluate specific clinical situations. Newer CT scanners with larger apertures and more rapid scanning time allow for imaging of patients even on life support systems.

MRI is limited by the high-strength magnetic field that can convert metallic iron-containing objects in their vicinity into dangerous missiles. At present, MRI is limited to patients who are reasonably stable and not on life support systems. The circumstances where CT and MRI are of proven clinical value can be considered anatomically.

### A. Mediastinum

The mediastinum and its contained large vessels are particularly well displayed on CT and MRI. Vascular injury or disruption are prime indications for transaxial imaging with CT or MRI. In most instances when a traumatic tear of the aorta is strongly suspected, the patient should undergo angiography without a CT or MR study. When the clinical suspicion of aortic injury is low, the patient can undergo a CT scan. If a mediastinal hematoma or infiltration of the mediastinum with blood is not detected, it is reasonable not to pursue the diagnosis of an aortic tear with aortography (34).

Suspected aortic dissection can be imaged with contrast-enhanced CT or

MRI with flow studies. When the patient is stable and good quality MR imaging available, this becomes the preferred method. However, CT (especially spiral CT) is an acceptable alternative for confirming the diagnosis and determining whether the ascending aorta is involved in the dissection. In many cases, aortography can be obviated.

Infection within the mediastinum, especially when associated with perforation of air-containing mediastinal viscera such as the esophagus or trachea, can usually be detected and localized with CT. In this circumstance, the oral administration of soluble, nonionic contrast material instead of barium will prevent spillage of barium into the mediastinum or pleura.

### B. Lungs and Pleura

CT of the thorax is a reasonably simple method of detecting the complications of lung trauma or infection in critically ill patients (35). Lung lacerations and hematomas are easily detected and differentiated from lung contusion. Lung abscesses or necrotic masses in an area of pneumonia are also quickly and easily identified. We have been struck by the frequency with which lung abscesses or empyemas can go undetected on conventional portable chest radiographs. The high frequency with which significant pleural effusions or pneumothoraces are missed on conventional chest radiographs, but detected with CT, has been emphasized (36).

In the SCU, complications related to tubes, catheters, and lines are not infrequent. CT has been shown to be a sensitive and accurate modality for detecting malpositioned chest tubes or fragments of catheters.

### C. Diaphragm

Diaphragmatic rupture is often overlooked because of the frequency of severe concomitant injuries to the patients. CT can be helpful in suggesting and often confirming the diagnosis of diaphragmatic rupture. Following intravascular administration of contrast material, abdominal organs such as the spleen or the stomach can be imaged herniating into the thorax through the diaphragmatic rent.

## VI. Ultrasound

Diagnostic and therapeutic chest sonography obtained on critically ill patients in an SCU has become commonplace. Most frequently it is used to explain abnormalities initially discovered on portable chest radiographs. Sonographic technology has multiple capabilities in the thorax. The most common of these is the evaluation of the opacified lung to distinguish between pleural fluid and lung masses. In addition to diagnosis, ultrasound is used in the thorax in the critically ill

patient to guide therapeutic maneuvers (37). These include the transthoracic aspiration of pleural fluid collections and the biopsy of pleural, chest wall, and lung parenchymal masses. In addition to these common uses of sonographic imaging of the thorax, other less frequent applications have been reported. Duplex sonography can image the axillary and subclavian arteries and veins, as well as the accessible portion of the superior vena cava for stenosis, obstruction, or thrombosis. Central venous catheters can be evaluated for pericatheter complications and patency. The recent introduction of transesophageal transducers has greatly expanded the bedside capabilities of the ultrasound examination. This section will detail the newest applications of ultrasound in the critically ill patient.

### A. Chest Sonography in Relationship to Other Imgaging Modalities

Portable chest radiographs are the most frequently used type of imaging study in the assessment of critically ill patients in an SCU. They are used for many purposes, including the assessment of the position of life support equipment (e.g., tracheostomy tubes), evaluation of the development of parenchymal infiltrates, atelectasis, effusion, and pneumothorax, and the exclusion of iatrogenic complications after interventional procedures (e.g., placement of central venous catheters, feeding tubes, thoracostomy tubes, and pacemakers and after surgical procedures). Chest CT scans have been shown to have many advantages over portable chest x-rays. However, the difficulty in transporting patients to the scanner and the cost, particularly for repeated examinations, limit its frequent use.

Chest sonography has several advantages over portable chest radiographs. It has high sensitivity for detecting pleural lesions and differentiating pleural disease from lung parenchymal disease. In fact, consolidated lung can be used as a sonographic window to visualize lesions not in continuity with the costal margins. Sonography at the bedside can accurately and easily guide aspiration biopsy of the subpleural lung as well as thoracentesis. In addition, the ease of this examination at the bedside makes it possible to do repeated examinations without danger. Compared to CT, sonography also affords a lower cost (38).

Nevertheless, chest sonography also has several disadvantages. The ultrasonic wave is unable to penetrate aerated lung or air in a pneumothorax or cavity. The sonographic examination is hindered by the requirement for an intercostal or subcostal acoustic window, and thus there is a restricted field of view of the lung. Interruption of sound wave transmission by air or the bony thorax results in many instances in poor visualization of the mediastinum, hila, and airways.

### B. Indications for a Bedside Sonographic Examination

Total or near-total opacification of a hemithorax in a patient unable to be easily transported to the CT scanner is the most frequent indication for a bedside

sonographic examination. A sonographic window for evaluation of the opacified hemithorax is obtained from either consolidated lung or pleural effusion. In the case of obstructed, atelectatic lung, the sonogram reveals a consolidation of the lung parenchyma with fluid within the bronchi (Fig. 7). Real-time sonography allows appreciation of the lack of air movement within the atelectatic lung segment. Consolidation frequently appears as a homogeneous, hypoechoic, wedge-shaped region of lung containing air within the bronchi. Movement of the region with respiration can be appreciated during real-time imaging and helps differentiate consolidated lung from pleural effusion.

Pleural effusions vary from single anechoic collections to heterogeneously echogenic collections containing complex septae and debris (Fig. 8). Pleural nodules can be identified on either the visceral or parietal pleura when pleural fluid is present. Pleural thickening has arbitrarily been defined as a pleural segment measuring more than 3 mm in thickness (39) (Fig. 9). McCloud and Flower (38) have described the utility of sonographic imaging of the pleura and emphasize that sonography can be performed with the patient recumbent or sitting. Sonography can also be combined with fluoroscopy for interventional procedures. Images may be obtained in sagittal, coronal, and axial planes.

Pleural fluid collections can be characterized by sonography as simple or complex, a differentiation that cannot be made radiographically (40). Sonography cannot only establish the presence of small amounts of fluid, but also guide aspiration of the fluid. Sonography is not, however, 100% specific for pleural fluid. Some pleural and chest wall tumors—notably lymphomas and neurogenic neoplasms—transmit ultrasound with few or no internal echoes and can be mistaken for a loculated pleural effusion. Ultrasound detection of pleural thickening is frequently limited when it is not accompanied by pleural fluid. Thin, linear structures, representing strands of fibrin floating in an anechoic mass and undulating with respiration, help distinguish a pleural fluid collection from a solid pleural mass. Sometimes the septae within an exudate are so profuse as to have a honeycomb appearance. This appearance often predicts significant difficulties with thoracostomy drainage.

Rarely, fluid collections are so complex as to present as a uniform mass of tiny echogenic structures that swirl with respiration. This is found with protein-rich exudates, such as empyemas, hemothorax, or occasionally with transudates caused by pleural-based malignancies. Sonography can also be revealing when a subpulmonic effusion gives the false appearance of an elevated hemidiaphragm. Similarly, sonography can show an inverted diaphragm, traumatic tears in the diaphragm, or the contents of a diaphragmatic hernia.

Ventilator-dependent patients in an SCU may have a paralyzed diaphragm. Rather than transporting the patient and all the life support systems to the fluoroscopic suite, bedside ultrasound can visualize the diaphragm and its range of movement.

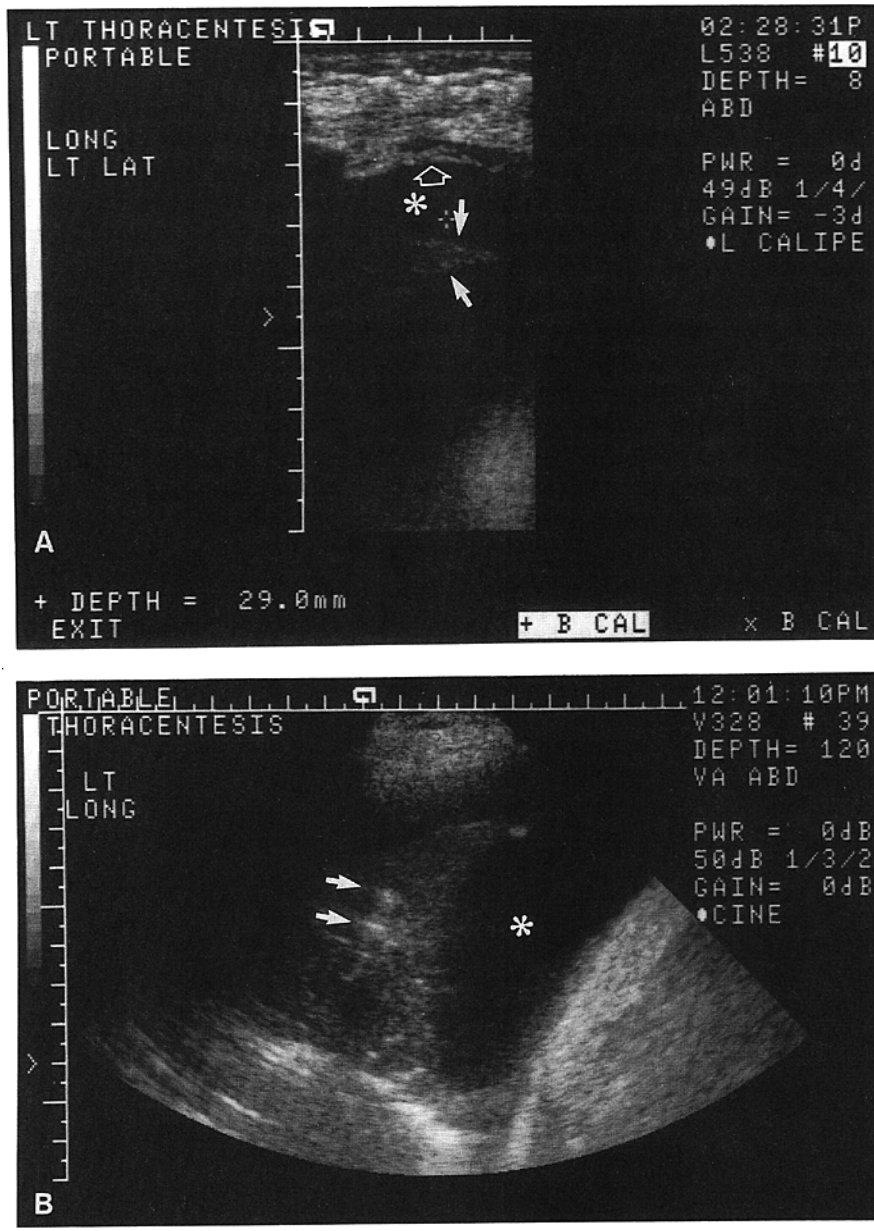


**Figure 7** Simple pleural effusions with atelectatic lung parenchyma. (A) Real-time high-resolution ultrasound of the lower thorax and chest wall shows a simple pleural effusion (asterisk) with a region of atelectatic lung containing fluid within bronchi (arrows). Note an uncalcified pleural plaque (open arrow). (B) High-resolution ultrasound image in a separate patient shows a simple pleural effusion (asterisk) containing a region of consolidated lung. The echogenic artifacts are from air within the bronchi (arrows).

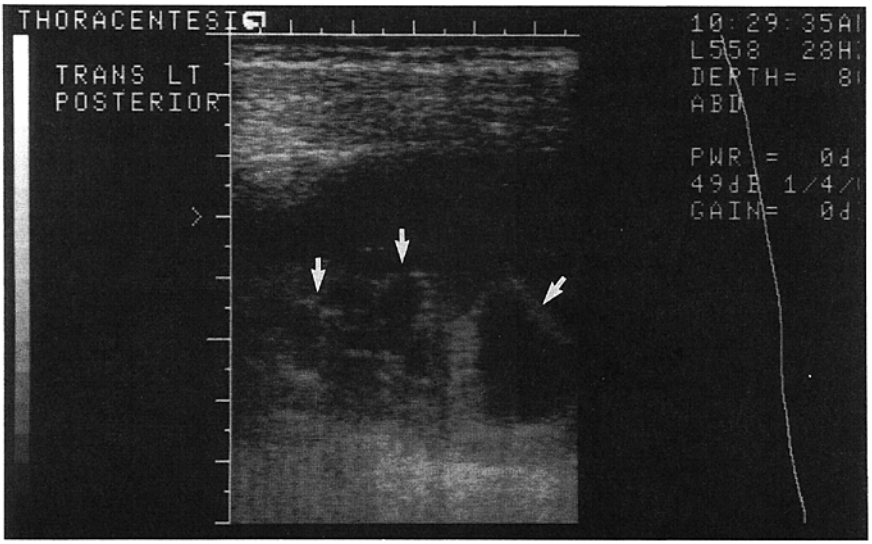


**Figure 8** Empyema with multiple septations. Real-time high-resolution ultrasound demonstrates a complex pleural effusion with multiple septations (arrows). Three thoracostomy tubes were required for drainage of the effusion. The septated nature of the empyema was not detected from chest radiographs.

### C. Ultrasound-Guided Pleural Interventions

Conventional thoracostomies are performed with a large-gauge tube (24–28 French), which is introduced via blunt dissection of the chest wall (39,41,42). This procedure is associated with a small but significant incidence of complications including laceration of the lung, diaphragm, liver, spleen, and stomach. The most important cause of failure of a thoracostomy tube is from malpositioning, blockage, or kinking of the tube. A multiloculated pleural fluid collection may require multiple drainage tubes or surgical decortication.

The two factors that preclude successful removal of pus, inflammatory exudate, or malignant effusions are a pleural peel and multiple loculations (43). Both of these can be demonstrated by ultrasound. Similarly, the portable ultrasound examination can image the therapeutic breakdown of fibrinous septae when a guide wire is used for this purpose.

Sonographically guided aspiration biopsy of pleural and parenchymal masses can be undertaken at the patient's bedside in an SCU (Fig. 10). Sonography provides safe and accurate real-time monitoring for either fine-needle aspirations or larger samples with a core biopsy system. Bronchi and larger vessels can be avoided during the biopsy, and the complication rate is minimal. Sonography

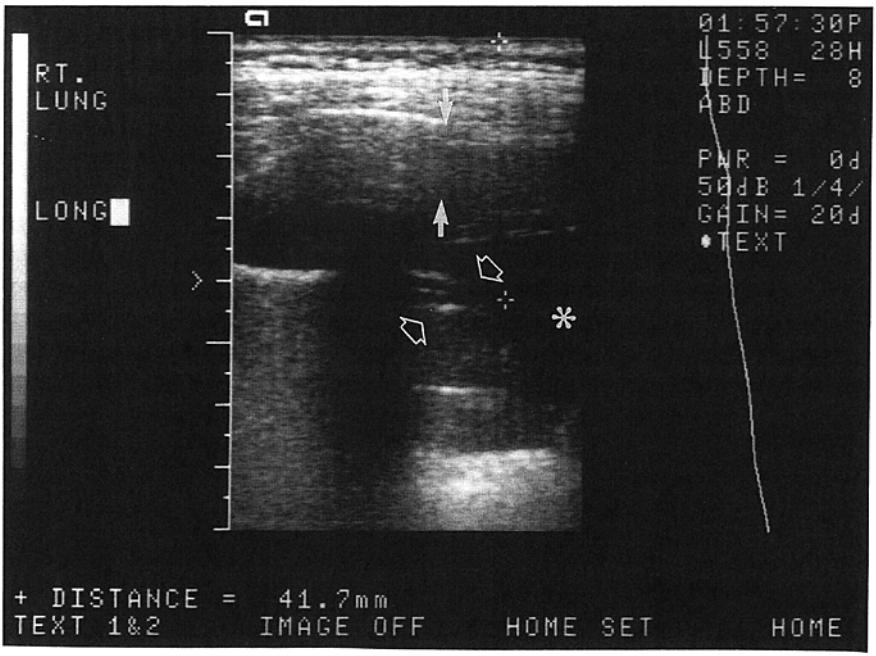


**Figure 9** Tuberculous empyema and pneumonia. Real-time high-resolution ultrasound shows marked thickening of the visceral pleura (between arrows). Atelectatic lung (open arrows) and small amount of pleural effusion (asterisk) contribute to the opacified hemithorax.

can enhance the likelihood of a successful thoracentesis, particularly when the fluid is loculated or small in quantity. When the diaphragm is inverted, it may be more difficult to distinguish the inferior margin of an effusion by sonography, particularly when peritoneal or pericardial fluid is present. Location of fluid posterior to the inferior vena cava indicates a pleural rather than a peritoneal site of the fluid. When low-level echoes are present within a pleural fluid collection, the fluid may simulate consolidated lung. Similarly, the presence of low-level echoes within a peripheral lung mass, such as an infarct or abscess, may mimic pleural fluid. Ultrasound can also be used for the optimal placement of a thoracostomy catheter for instillation of sclerosing agents, particularly if the fluid collection is loculated (44,45).

### D. Duplex Doppler Ultrasound

The anatomy and patency of major central veins can be identified with duplex doppler ultrasound before or during the placement of indwelling catheters (46).

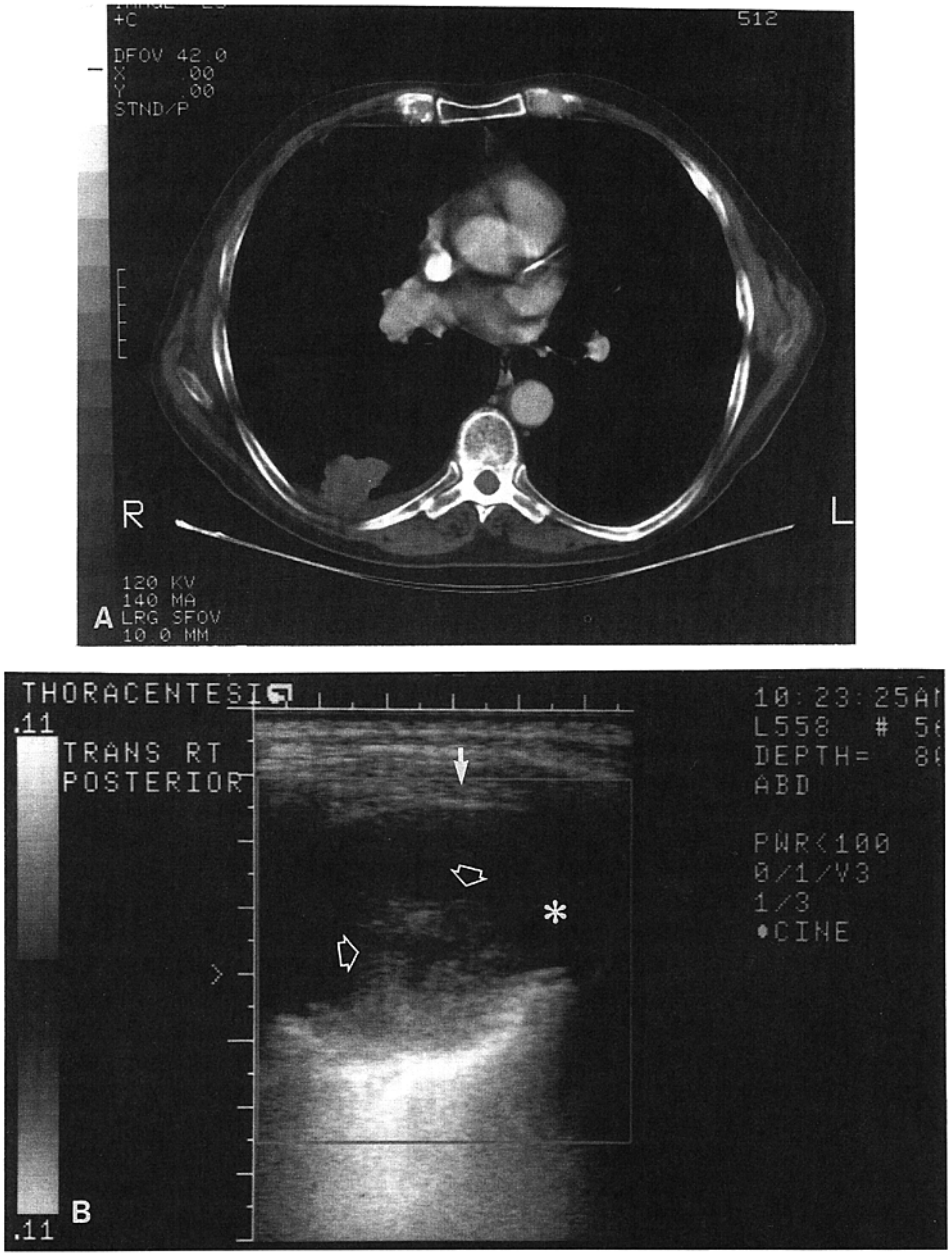


**Figure 10** Metastatic squamous cell carcinoma producing a pleural-based mass. (A) CT of the lower thorax demonstrates a pleural-based mass with adjacent pleural thickening. The mass is inhomogeneous, suggesting necrosis. (B) High-resolution sonogram of the right posterior chest demonstrates the pleural thickening (arrow). A small pleural effusion (asterisk) and a solid tumor mass with central necrosis (open arrows) produces a low echogenic focus. Biopsy used ultrasound guidance.

Central venous access for catheters may be difficult in patients who have had previous central lines or complications from them. Similarly, doppler ultrasound can evaluate pericatheter abnormalities, such as aneurysms, hematomas, and abscesses. Thrombosis and obstruction or stenosis of central veins, including portions of the visually accessible superior vena cava, can be imaged with transcutaneous sonography (47–49). Other vessels in the neck that can be imaged include the extracranial carotid system, which can be imaged with a bedside examination for suspected stenosis or explanation of the cause of a bruit. When the vertebrobasilar system is the suspected site for abnormality, the vertebral arteries can be evaluated both for patency and direction of blood flow.

### E. Future Applications

An important developing application for sonography in the critically ill patient in an SCU is transesophageal ultrasound (50). Transesophageal sonography markedly extends and complements the capabilities of transthoracic echocardiography. Because of its simplicity and precision, transthoracic echocardiography is the examination of choice for demonstrating the structure and function of the heart. It can be readily performed at the bedside and it can easily be repeated on multiple occasions. Real-time imaging of the heart is augmented by color-flow doppler, and spectral information is now available with most echocardiographic units. This modality provides both detailed anatomical as well as hemodynamic information about the heart and great vessels.

In acutely ill patients with shock, severe heart failure, chest pain, or sepsis, echocardiography is frequently able to explain the cause of the patient's findings. The cause can be acute myocardial infarction, ventricular aneurysm, acute valvular dysfunction, endocarditis, prosthetic valve malfunction, cardiac tamponade, aortic dissection, or even myocarditis.

Transthoracic echocardiography is limited by the requirement for an acoustic window. Usually, the transducer is applied and the ultrasound beam directed at the heart through the intercostal, substernal, suprasternal, or subcostal spaces. Emphysema, obesity, abdominal distension, narrow intercostal spaces, and calcified rib cartilages are just some of the anatomical factors that can impede the echocardiographic evaluation of the heart. In the postsurgical patient, surgical drains and dressings, as well as mediastinal tubes, pacemaker wires, and air in the mediastinum and subcutaneous tissues can also interfere with transthoracic echocardiography.

Many of the difficulties with transthoracic echocardiograms can be overcome by the newer transesophageal echocardiogram. An ultrasound transducer is mounted at the tip of a flexible endoscope, which is introduced into the esophagus. Virtually no impending structures interpose between the esophagus and the heart, and images are exquisite in clarity and detail. In fact, anatomical details that are

seldom seen by conventional transthoracic echocardiography are easily appreciated, including the proximal coronary arteries, atrial appendages, and pulmonary veins. Some of the present indications for transesophageal echocardiography include suspected acute aortic dissection, cardiac tamponade, unexplained shock, prosthetic cardiac valve dysfunction, intracardiac thrombus or tumor, endocarditis, and interoperative monitoring of cardiac ischemia during cardiac surgery (51,52) (Fig. 11).

Transesophageal echocardiography is not hindered by scatter from the hardware of prosthetic valves during evaluation for intracardiac thrombi. Similarly, thrombi in the left atrium are frequently located in its appendage, which is not easily imaged during most conventional transthoracic echocardiograms. On the other hand, transesophageal echocardiography easily visualizes the atrial appendages (53) (Fig. 12).

Cerel and Burger (54) describe a patient with an acute inferior wall myocardial infarct who underwent percutaneous coronary angioplasty. The patient subsequently experienced a cardiac arrest with severe hypoxia. A pulmonary angiography was not helpful. The transesophageal echocardiography demonstrated a large right pulmonary artery thrombus. Transesophageal echocardiography also could monitor the resolution of the thrombus during anticoagulant therapy.

Font and colleagues (55) compared transesophageal echocardiography to transthoracic echocardiography in 112 studies performed in an SCU. The transesophageal approach detected 131 significant findings, compared to only 95 for the transthoracical route. Transesophageal echocardiograms also were superior in patients with significant mitral regurgitation and added information in evaluating valvular vegetations, intracardiac masses, intracardiac thrombi, and congenital heart disease. They recommend transesophageal echocardiography for assessing ventricular function in all patients not amenable to the transthoracic approach. They also advocate its use in critically ill patients with unexplained cerebrovascular accidents to detect congenital intracardiac shunts. They conclude that standard transthoracic echocardiography has a higher percentage of false-negative studies than the transesophageal route and the latter imaging modality often provides additional significant clinical information.

Pearson and associates (56) evaluated the results of 62 transesophageal examinations performed in an SCU. All patients had initially undergone transthoracic echocardiography. In most cases, the transesophageal study was obtained because of a technically suboptimal transthoracic examination. Diagnoses that were missed by surface echocardiography included aortic dissection, left atrial thrombus, ruptured papillary muscle, and prosthetic valve vegetations. They reported no serious complications for the transesophageal study. They propose that major indications for performing transesophageal echocardiography in an SCU should also include patients with myocardial infarction for potential complications. In their study, two cases of papillary muscle rupture were clearly demon-

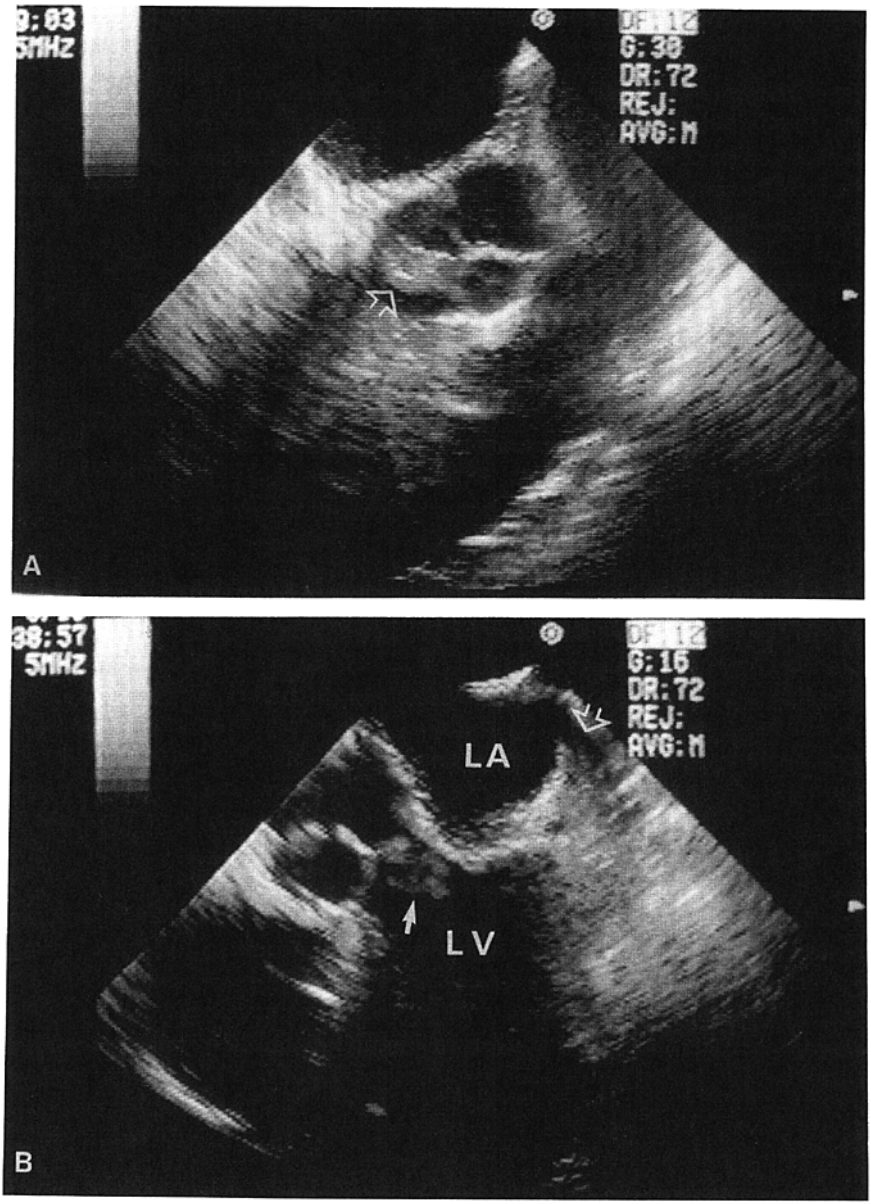


**Figure 11** Vegetation on an aortic valve. (A) Transesophageal sonogram through the aortic valve demonstrates an infected thrombus on the non-coronary cusp of the aortic valve (open arrow), in a patient with endocarditis. (B) Transesophageal sonogram in an oblique plane shows the left atrium (LA) with its atrial appendage (open arrow). Posterior to the atrium is the aortic valve and root with the thrombus (arrow) protruding from the valve into the outer tract of the left ventricle (LV). (Courtesy of Dr. Greg Schwartz, Veterans Administration Medical Center, San Francisco, California.)

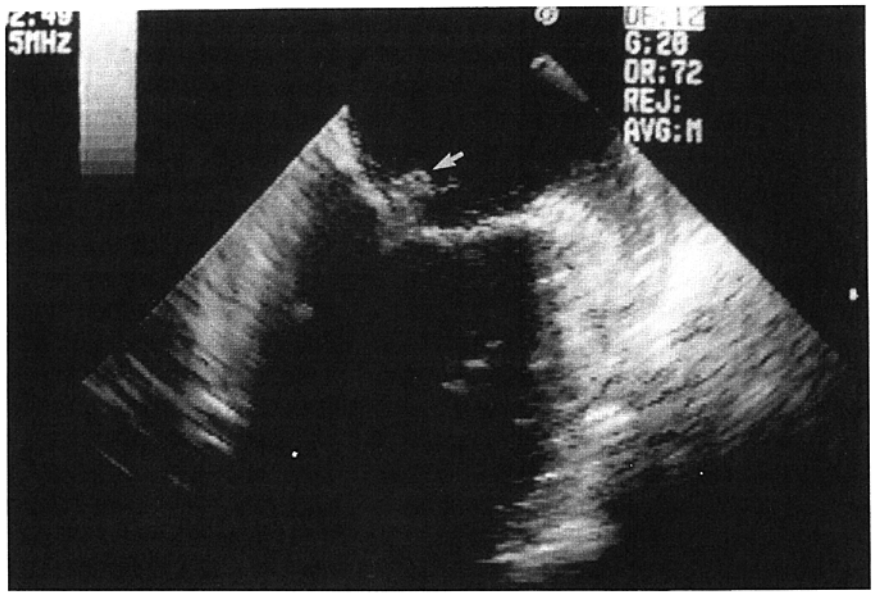


**Figure 12** Vegetation on a mitral valve. Transesophageal sonogram through the mitral valve shows a vegetation (arrow) in a patient with endocarditis. Note visualization of the left atrial appendage, normally not seen with transcutaneous echocardiography. (Courtesy of Dr. Greg Schwartz, Veterans Administration Medical Center, San Francisco, California.)

strated by transesophageal echocardiography, which facilitated prompt surgical therapy. Transesophageal echocardiography was also useful in assessing segmental and global left ventricular function and detecting intracardiac shunts.

Omoto and colleagues (57) have assessed other miscellaneous conditions with a biplane transesophageal probe. These include a left ventricular myxoma, constrictive pericarditis, mediastinal tumor, and lung cancer. Rao and associates (58) describe the localization of a Kimray-Greenfield filter that had migrated into the pulmonary artery and was imaged by echocardiography. Hausmann and coworkers (59) described transesophageal echocardiography following lung transplantation for the evaluation of the pulmonary artery and vein anastomoses. Thrombosis of the pulmonary vein and stenoses of the pulmonary artery anastomosis were easily diagnosed by transesophageal echocardiographic examinations and confirmed by cardiac catheterization and pulmonary angiography.

Savino and colleagues (60) have applied transesophageal two-dimensional and doppler echocardiography to estimate pulmonary artery blood flow, which is equivalent to cardiac output. Similarly, Muhiudeen and associates (61) suggest the use of interoperative transesophageal pulsed doppler echocardiography to monitor

cardiac output in patients undergoing cardiovascular surgery, particularly for valvular disease.

In a study performed in the critical care units of the University of California San Francisco, Foster and Schiller (62) determined that unexpected findings in 21 of 83 instances led to a change in management in 17% of 69 patients evaluated. Nineteen percent of these patients underwent surgical intervention without any further examination, and 22% had further evaluation by a more invasive technique. No significant complication were attributed to the transesophageal examination.

The main contraindications for the use of transesophageal echocardiography include esophageal pathology such as varices, strictures, esophagitis, scleroderma, upper gastrointestinal bleeding, dysphasia, and a history of esophageal surgery or mediastinal radiation. Patients with a history of these esophageal diseases should first be endoscoped by a gastroenterologist. A theoretical concern with transesophageal echocardiography is that a left atrial myxoma could embol-

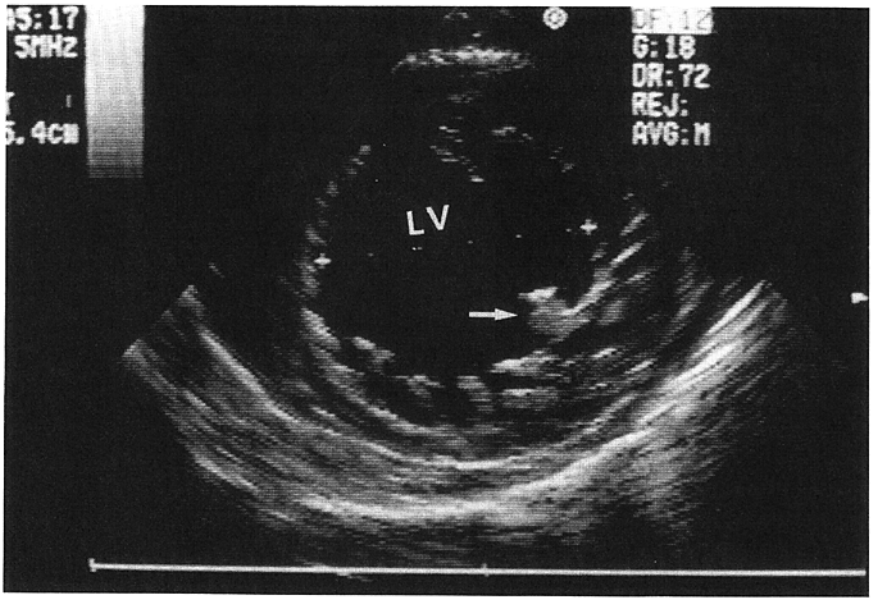


**Figure 13** Normal cardiac structures. Transverse, short-axis transesophageal echocardiogram through the left ventricle (LV) demonstrates the ease with which the wall and luminal measurements can be achieved. The origin of a papillary muscle (arrow) is demonstrated. (Courtesy of Dr. Greg Schwartz, Veterans Administration Medical Center, San Francisco, California.)

ize during insertion of the esophageal probe due to pressure from the transducer. Patients who are at increased risk or aspiration, including pregnant women, should have their airway protected before probe insertion, especially if sedation has been administered.

Complications of transesophageal echocardiography occur in less than 1% of cases. Esophageal perforation, the major complication, occurs in about 0.02% of studies. Reports of dysrhythmias, bronchospasm, and temporary vocal cord dysfunction are uncommon. Other complications are from adverse reactions to the drugs used for sedation (62,64).

Future development in transesophageal echocardiography include instruments with smaller tips, and transducers incorporating multi-planar and 360 degree imaging. The applications of transesophageal echocardiography are largely qualitative at present. In the near future, continuous-wave doppler echocardiography with computer analysis should allow quantitative measures of regional wall motion and individual heart chamber pressures, volumes and function (Fig. 13).

## VII. Imaging Equipment in the Future Special Care Unit

The following features should be considered for any institution that is planning or equipping a special care unit expected to be operational in the twenty-first century.

1. Most regular imaging will be digital. A busy intensive care unit or group of special care units should have on-site capability of reading the computed radiographic plates for digital imaging. Once digitized, the images can be displayed simultaneously on high resolution monitors in an SCU and in a central radiology department for interpretation. Whether the images are finally stored on hard copy or on an optic disc is not of importance. The x-ray equipment will be either ceiling-mounted x-ray tubes that can be extended to all beds, or portable x-ray units that are resident in the SCU.
2. Ultrasound capabilities will be immediately available in the SCU. Each SCU will have a dedicated ultrasound machine and the SCU personnel will be capable of using the equipment for such things as insertion of central lines, detection of pleural or peritoneal fluid or air, and even detection of deep venous thrombosis in the legs.
3. A dedicated fluoroscopic suite will be immediately available to an SCU. Special care units will be routinely equipped with beds that can be easily maneuvered within the confines of fluoroscopic units.
4. CT and MR will be utilized with increased frequency, especially in those circumstances shown to be beneficial. Hardware and monitoring devices will be modified to be used in MR scanners. Newer MR units

with a shorter bore and wider aperture will allow for easy access to patients, even on life-support systems.

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# 32

# Lung Transplantations

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## I. Introduction

In the last 20 years, transplantation of the kidney, liver, and heart has become an important therapeutic option for patients with irreversible failure of these organs; clinical application of lung transplantation has evolved more recently. This chapter summarizes current knowledge and practice, with special emphasis on some new important or unresolved specific topics.

## II. Surgical Procedure

### A. Selection and Management of Organ Donors

A successful pulmonary transplantation program relies on the optimal selection and harvesting of allografts from suitable perfused organ donors (1). However, the shortage of organ donors remains a major limitation to the activity of most clinical transplant centers (1). This also explains why 25% of the patients entered into an active waiting list die while waiting for a suitable pulmonary transplant (2). It has been estimated that only 20–30% of potential donors are actually used and that only 5.2% of perfused organ donors are suitable for lung transplantation (3),

strengthening the notion of lung vulnerability to trauma or indirect injuries (aspiration, infection, or edema).

The donor lungs are usually considered suitable for transplantation if they fulfill the following selection criteria (4,5,21):

1. Age below 40 or 55 or less than 65 for a lung and less than 45 years for a heart-lung transplant.
2. A normal chest radiograph or one with minor changes. Previous x-rays should be reviewed (when available). A chest radiograph done within 2 hours of organ harvesting is also necessary to make sure that new abnormalities have not appeared.
3. A normal bronchoscopic examination is mandatory to eliminate an unsuspected aspiration or primary lung infection. However, a minor bronchial contamination should not be a contraindication to organ harvesting: successful lung transplantations have been conducted when donors were pretreated with broad-spectrum antibiotics before organ extraction and when recipients were treated with specific antibiotics as soon as the Gram stain and cultures from washings drawn from both sides of the donor lungs were available.
4. Adequate gas exchange is necessary, assessed by an oxygen tension–inspired oxygen concentration of at least 300 mmHg or a $Pao_2 > 300$ mmHg with $Fio_2$ of 1.0 and PEEP of 5 cm $H_2O$.
5. No history of prior significant cardiopulmonary disease, no pulmonary or systemic infection, no severe chest trauma, and no prolonged cardiocirculatory arrest.
6. A negative screening for hepatitis B and HIV infection. Regarding cytomegalovirus (CMV) serological status, efforts should be made to match donor and recipient. Because of the shortage of donors, however, those with previous CMV infection are generally not excluded in most centers (4).
7. ABO compatibility (or better ABO identity), since the use of ABO-compatible but not identical donors may result in the development of potentially severe hemolytic anemia.
8. Size matching, accomplished by comparing the predicted lung volumes (total lung capacity, forced vital capacity) of the potential donor and recipient, calculated by established formulas taking into account the measured height, age, and sex. Chest measurements of the donor and recipient on chest x-rays are less reliable.

The first lung transplantation from a living donor (mother to child) was performed at Stanford University in October 1990 (6). The use of living donors must be limited for the moment, since serious risks exist for the donor even though they can be reduced by using a single lobe rather than a whole lung. Furthermore,

long-term follow-up of recipients with lobar transplants from living donors is presently unavailable.

The general shortage of organ donors requires the use of optimal donor-management strategies in order to maintain all potential transportable allografts in their best functional state: contrary to the volume repletion used to maintain a high adequate urine output in kidney donors, the maintenance of adequate lung function relies on volume restriction. Indeed, intravenous fluids should be limited as much as possible in order to obtain

Urinary output of 1–2 ml/kg/min
Mean systemic arterial pressure $\geqslant$ 70 mmHg
Central venous pressure or capillary wedge pressure of, respectively, 10–12 $cmH_2O$ and 12–14 mmHg.

Donors should be mechanically ventilated with tidal volumes of 15 ml/kg and a PEEP of 5 $cmH_2O$; using these parameters, $Paco_2$ is usually normal, $Pao_2$ is maintained at 90–100 mmHg with the lowest inspired oxygen concentration as possible, and peak inspiratory pressure should not exceed 25 cm $H_2O$. During this period of donor maintenance, it is mandatory to reassess the chest x-ray and gas exchange every 2–3 hours. It is fairly common that an initially acceptable donor's lung must be rejected later.

The Toronto Group, between November 1983 and May 1991 (4), harvested pulmonary allografts from 93 donors. This pool provided allografts for 55 single and 44 double lung transplantations, and only 25% of the organ procurement was carried out at the general division of the Toronto Hospital. These 93 donors were harvested for cardiac ($n = 55$), hepatic ($n = 68$), and renal ($n = 86$) grafts. The mean donor age (52 males and 41 females) was 30 ± 11 years (range: 11–60). Acute brain disease and trauma were the cause of death in 97% of the donors. The mean $Pao_2$ of these patients on 100% $O_2$ and 5 $cmH_2O$ PEEP was 465 ± 100 mmHg (range: 300–597). The mean ischemic time was 3.53 ± 1.25 hours (range = 1.10–8.52). In only 16 of 91 transplantations, both recipient and donor were negative for CMV.

### B. Transplantation Technique in Recipients

Between 1981 and 1985, more than 500 successful heart-lung transplantations (HLT) have been carried out in patients with irreversible and severe pulmonary hypertension related to Eisenmenger's syndrome or primary pulmonary hypertension (7); indications for HLT have been more recently extended to patients with end-stage parenchymal lung diseases (8). In HLT, the normal anastomoses between coronary and bronchial arteries are not disrupted (5) and healing of tracheal anastomosis is subsequently of better quality.

Double lung transplantation (DLT) has been proposed for patients with

suppurative lung disease or those with obstructive lung diseases as well as in primary pulmonary hypertension when cardiac ventricular function is adequate (9). To avoid the frequent ischemic airway complications, the technique of tracheal anastomosis has been modified by using two main bronchial anastomosis (10). Recently, these bilateral single lung transplantations have been performed successfully via either a transverse thoracosternotomy or two lateral thoracotomies (11). In the latter case, a cardiopulmonary bypass is not always necessary. In order to optimize organ supply, the native heart of the recipient can be transplanted into another cardiac recipient (domino procedure) (12).

It is only since 1983 that single lung transplantations (SLT) have been successfully performed. This procedure was initially restricted to patients with end-stage fibrotic lung diseases (13). Indications for SLT have been further extended to patients with emphysema (13) as well as chronic pulmonary vascular diseases (14). SLT had not previously been considered feasible in patients with emphysema because of the subsequent risks of ventilation perfusion imbalance in the transplanted lung. Recently, however, some experimental and clinical studies have shown that a satisfactory matching of ventilation to perfusion usually occurs in the allograft unless rejection or infection develops in the transplanted lung (15–17). SLT offers several advantages: better potential organ availability, since the heart and two lungs from a single donor can be transplanted into three different recipients (although this is not often achieved) (18), and a lower risk of operative and postoperative bleeding. Its disadvantages are related to the native lung and the concern about the low functional reserve in case of rejection or infection, about potential lower long-term improvement in functional capacity, and finally about the frequent unsatisfactory healing of bronchial anastomosis (9,19). This latter complication is not improved by using bronchial wraps (5), and their use is no longer recommended.

After organ recovery, the donor's lungs are usually flushed with the donor blood or Eurocollins solution and then maintained in cold Eurocollins solution, allowing preservation of the lungs for 6–8 hours. This lung preservation time could be extended in the future.

### C. Immunosuppressive and Antimicrobial Therapy

Cyclosporin A, which selectively and reversibly inhibits immunocompetent T lymphocytes, is prescribed in all protocols as the first-line treatment to suppress graft rejection (20). Cyclosporine is given orally at a maintenance dose of 6–10 mg/kg/day to ensure a whole blood through level of 200–600 mg/ml with a serum creatinine level less than 120 μmol/L. Azathioprine is usually given in oral doses of 1–2 mg/kg/day, in order to keep the total white blood cell count above $5.0 \times 10^9$ per liter (21). Some physicians add low doses of prednisone to their maintenance protocols. Others use $OKT_3$ or antilymphocyte globulins during the immediate

postoperative period. It has been recently shown (22) that patients treated with an immunosuppressive regimen including cyclosporine, azathioprine, prednisone, and rabbit antithymocyte globulins for the first 5 postoperative days suffered a significantly lower number of acute rejection episodes compared to patients treated with cyclosporine, azathropine, and prednisone alone (2.1 vs. 3.1 episodes per patient). However, this did not lead to any difference in terms of survival, grade of rejection, or airway flow limitation.

Patients commonly also receive long-term prophylaxis with a combination of sulfamethoxazole and trimethoprim as well as nystatin and acyclovir (23). In patients with cystic fibrosis, the donor and recipient receive a third-generation cephalosporin and either antipseudomonal penicillin or aminoglycoside for 7–10 days (24).

## III. Patient Selection Criteria

Patients with untreatable end-stage cardiopulmonary disease without any other severe systemic disease but a limited life expectancy, a major limitation in daily activities, a potential for rehabilitation, and an acceptable nutritional status are the best candidates for lung or heart-lung transplantation. Patients over age 60 are not usually accepted, but in some programs this age has been extended to 65, particularly for SLT. A thorough individual evaluation is mandatory in such patients in order to rule out some associated disorders such as an occult malignancy or a coronary artery disease by means of a systematic left heart catheterization with coronary angiography. In each case, the biological rather than the chronological age must be taken into account (25). A history of malignancy is generally regarded as an absolute contraindication with the exception of a few cases, for instance, young patients presenting with isolated and unresectable pulmonary metastases occurring after a long disease-free interval. Patients with a history of connective tissue disease (CTD) may be candidates if their involvement is limited to the lung. Diabetic patients can also be selected if their disease is mild, often induced by the administration of corticosteroids. Some previous absolute contraindications are no longer considered as such, e.g., patients with a previous history of thoracic surgery or long-term therapy with corticosteroids; in this latter case, however, if it is not possible to taper the daily dose below 10–15 mg of prednisone, it seems more reasonable to give up the lung transplantation (23,26). Other exclusion criteria include tobacco, alcohol, or other drug addiction, psychosocial problems, or an expected poor compliance to further medical therapy. All of these exclusion criteria have to be considered because of the limited supply of organ donors, the large number of patients on the waiting lists, and the heavy cost of lung transplantation.

Candidates for SLT are patients free of chronic pulmonary infection suffering from irreversible, life-threatening obstructive or restrictive lung disease, as

well as patients with primary pulmonary hypertension. Patients with irreversible chronic lung disease and infection (cystic fibrosis or bronchiectasis) will need at least a double lung transplantation. Finally, heart-lung transplantation is indicated when there is an uncorrectable structural heart disease associated with end-stage pulmonary disease. Historically, heart-lung transplantation has been the first effective and successful transplantation in patients with cystic fibrosis or primary pulmonary hypertension.

Selection criteria are fairly well defined in patients with primary pulmonary hypertension whose median survival is 2.8 years (27) after diagnosis and in whom mortality is tightly correlated with a marked limitation in physical activity, the presence of Raynaud's phenomenon and severe hemodynamic variables (26). In patients with cystic fibrosis, a variety of factors has been also found to correlate with mortality: frequency of hospital admissions, antimicrobial therapy, weight loss, and the degree of respiratory function impairment ($FEV_1 < 30\%$ of predicted values, $Pao_2$ and $Paco_2$ while breathing room air below 50 mmHg or above 55 mmHG, respectively) (26).

Selection criteria are much more difficult to establish in patients with other chronic obstructive pulmonary diseases and idiopathic pulmonary fibrosis. The degree of disability, poor exercise tolerance, severe physiological disturbances ($FEV_1$, $Pao_2$, $Paco_2$, PAP) and the characteristics of abnormalities on chest x-ray or CT scan and their extent are generally taken into account (28).

## IV. Results

### A. Survival

The registry of the International Society for Heart and Lung transplantation (29) had recorded more than 2200 lung transplantations worldwide as of December 31, 1991. There were 1212 HLT, 716 SLT, and 289 DLT, with a 1-year actuarial survival rate of, respectively 59, 69, and 62%. The most common underlying diseases were pulmonary fibrosis, emphysema, cystic fibrosis, and pulmonary hypertension. The median age of transplant recipients was 44 years (range: 1–67 years), and the most commonly transplanted group comprised patients aged 41–50 years (30).

When reporting results on their first 100 transplantations (57 HLT, 34 DLT, and 9 SLT), The Paris-Sud University Lung Transplant Group gave actuarial survival rates of 65, 49, and 46% at 1, 2, and 3 years, respectively. Results were very close for HLT (7, 52, and 49% at 1, 2, and 3 years) and DLT (64, 50, and 42%).

Two recent studies have reported better 1-year survival rates for either SLT or DLT with, respectively, 77–90% and 82% (23,31). The actuarial survival at 1 year has improved over time: 50.4% before January 1, 1989, and 68.7% thereafter.

Prognosis may also depend on the primary disease for which lung transplan-

tation has been performed. Survival rates in lung transplant recipients for pulmonary fibrosis or chronic obstructive pulmonary diseases are very close (68.3 and 68.4% at 1 year, respectively). For cystic fibrosis, survival seems to depend on the transplantation procedure itself, with 57% survivors at 1 year for DLT versus 42% for HLT in North America (30), and on the transplantation center, with a 42 versus 78% 1-year survival rate for HLT (32). Factors that can influence early and late mortality have been studied by the group of Papworth, which reported that among 100 HLT recipients (1984–1991), 17 had died early (<3 months) and 25 late (>3 months). The major cause of early death was CMV infection in 8 of 17. Significant predictors of mortality were intubation time, reintervention, blood loss, postoperative complications, and finally CMV matching between donor (D) and recipient (R), with an 8% mortality rate for D-, R- and 22% for D+, R+ patients. Causes of late deaths were obliterative bronchiolitis in 17 and infections in 8 cases. Individually, factors that influenced late mortality were the number of acute rejection episodes within the first 3 months after transplantation and a serum creatinine level of less than 181 mmol/L at 3 months.

### B. Morbidity

#### *Acute Rejection*

Though this can occur at any time during follow-up, acute rejection appears most commonly during the first 3 months after transplantation, with a 50–87% estimated incidence (33). Acute rejection is most often revealed by clinical symptoms: cough, dyspnea, fever. In 15% of patients, however, acute rejection is symptom-free (34) and the diagnosis is considered in the face of radiographic abnormalities (interstitial shadowing, air space consolidation, or pleural effusion) or when laboratory lung function testing or daily home spirometric monitoring show a decrease in $FEV_1$ or FVC of more than 10% (35). These findings are not specific for lung rejection and can be found in cases of infection or adult respiratory distress syndrome (36).

For some authors, the diagnosis is established on the basis of a favorable response to an intravenous pulse dose of methylprednisolone leading to a prompt decrease of fever and radiographic infiltrates and by an improvement in oxygenation and dyspnea over a 12- to 24-hour period. Other teams prefer confirmation of the diagnosis prior to therapy by means of transbronchial biopsies showing histological features of rejection with perivascular mononuclear infiltrates more or less extending into alveolar septa (37). The role of transbronchial lung biopsies in the diagnosis of acute lung rejection is now well defined, with a high degree of sensitivity and specificity when several biopsies (3–4 specimens) are taken on each occasion (38).

Endomyocardial biopsies are no longer carried out in HLT recipients, since isolated cardiac rejection is rare and rejection of the lung commonly occurs without simultaneous cardiac rejection (34). Treatment of acute rejection is usu-

ally achieved by a transitory increase in the immunosuppressive regimen leading to a rapid improvement.

*Infection*

The first cause of early mortality (<3 months) is infection. Bacterial pneumonia is common, favored by immunosuppressive therapy and, in the long-term postoperative period, by chronic rejection. Antimicrobial therapy is usually effective when directed against *Pseudomonas* spp., *Staphylococcus aureus*, *Haemophilus influenzae*, *Staphylococcus pneumoniae*, and sometimes *Legionella pneumophila*.

CMV is the most common cause of infection 4–8 weeks postoperative. In clinical practice, one currently distinguishes CMV infection from CMV disease as follows (36):

- CMV infection is asymptomatic and diagnosed on the positivity of biological tests such as serology and/or culture of blood, urine, saliva, or bronchoalveolar lavage. Primary CMV infection is very likely considered when there is a fourfold rise in IgM antibodies or an inhibition in competitive ELISA >50% (75). CMV reinfection may be discussed when there is a fourfold increase in CMV antibody compared to pretransplantation values.
- CMV disease is associated with symptoms such as fever, hepatitis, leukothrombocytopenia, or pneumonitis. The diagnosis of CMV pneumonitis is established when several of the following data are associated: a positive culture for CMV from bronchoalveolar lavage, the presence in bronchoalveolar lavage or transbronchial biopsies of cells containing typical nucleic and cytoplasmic viral inclusions ("owl eye"), and lung infiltrates on chest radiographs.

The rate of CMV infection is affected by the serological matching initially between the recipient and donor and later between the recipient and eventual blood donors. In the Papworth experience (39) the reported incidence of CMV infection was 78% in antibody-negative HLT recipients receiving organs from CMV antibody-positive donors (D+, R−) but was only 20% in D−, R− patients. All D+, R+ patients experienced CMV reactivation or reinfection, which occurred in only 57% of D−, R+ patients, in the series from Papworth (39) and Pittsburgh (40), the frequency and severity of CMV disease were greater in CMV-positive recipients (32%).

### C. Pulmonary Function Tests and Exercise Tolerance

HLT and DLT recipients who survive the first 6 postoperative months and who remain free of complications return to a normal ventilatory lung function ($FEV_1$) in more than 80% of cases (41–43). After SLT, a restrictive or obstructive

ventilatory defect sometimes persists, depending on the underlying disease in the native lung (restrictive or obstructive). Following lung or heart-lung transplantation, arterial blood gases at rest return to normal or near-normal values (14, 41,42,44).

In the results of the Paris-Sud University Lung Transplant Group, and for the 26/57 surviving HLT patients at 1 year, the values for VC, $FEV_1$, and $V_{25-75}$ were, respectively, 83 ± 17, 71 ± 29, and 60 ± 47% of predicted values. Three years after transplantation and for the 13/57 survivors, these values were 91 ± 17, 81 ± 28, and 70 ± 43%, respectively. Values for patients with DLT in the 12/34 survivors at 1 year were quite similar: VC, 85 ± 23%; $FEV_1$, 81 ± 29%; and $V_{25-75}$, 83 ± 42% of predicted values.

All transplanted patients improve their exercise performance. However, their maximum workload and maximum oxygen consumption usually remain below normal values (42,45,46). Deconditioning is the most likely explanation for such persistent abnormalities. SLT and DLT recipients significantly improve their exercise tolerance as well, judged on a 6-minute walking test postoperatively (300 and 600 m, respectively) (47).

The group of Beaujon (Paris) studied 16 patients after single lung transplantation for severe obstructive lung disease who had survived for at least 6 months. Before transplantation, the patients overall had severe obstruction with $FEV_1$ 17 ± 6% of predicted, $PaO_2$ 51 ± 10 mmHg, $PaCO_2$ 49 ± 11 mmHg, and a 6-minute walking test 99 ± 84 m. A significant functional improvement was observed postoperatively with patient $FEV_1$ at 3 months reaching 53 ± 13%, $PaO_2$ 81 ± 3 mmHg, and $PaCO_2$ 39 ± 3 mmHg. After 6 months, the distance covered during 6 minutes had risen to 587 ± 147 m.

### D. Quality of Life

Two studies using the Nottingham Health Profile have shown that after transplantation for cystic fibrosis, patients had a significant improvement in physical mobility and energy during five of seven daily life activities (41,48).

## V. Retransplantation

Retransplantation has been proposed in patients with unsuccessful single lung transplantation because of acute airway necrosis, severe and untreatable stricture of the airway, and/or obliterative bronchiolitis. Despite considerable pressure arising from the patient and family, most transplant teams are reluctant to offer a second transplant to a former recipient. The much lower survival rate following retransplantation is the main reason for such reluctance. The International Transplant Registry in St. Louis reported 39 cases of retransplantation among 618 single lung transplantations performed worldwide between 1983 and 1991. Seventeen of

these patients had early retransplantation (less than 2 months after first transplantation) with a 53% mortality rate (9 deaths). Twenty-two patients underwent a late retransplantation (more than 2 months after first transplantation) with an overall mortality rate of 60% (49).

Results of retransplantation in the Toronto group are similar with, among 51 SLT and 31 DLT former recipients, 4 early retransplantations (3 deaths) for acute tracheal necrosis and 5 late retransplantations (3 deaths) for untreatable bronchial strictures or obliterative broncholitis (49).

## VI. Specific Topics

### A. Airway Complications

Airway complications have been reported in about 5–10% of heart-lung and en-bloc double-lung transplantation (50,51). After single lung transplantation, airway complications are more frequent because in the first postoperative weeks bronchial blood supply depends entirely on retrograde collateral flow from the pulmonary to the bronchial circulation. Therefore, any graft dysfunction will reduce this collateral flow, resulting in bronchial ischemia. Heart-lung transplantation has the potential advantage of collateral blood supply to the airway via coronary to bronchial arterial connections. In fact, the incidence of airway complications may reach 10–12% after single-lung transplantation (51–53) as found in all types of lung transplantation. Curiously, these complications were frequent in our first 10 single lung transplantations, but this incidence decreased significantly with no change in perioperative immunosuppressive strategies or surgical technique.

The omentum, intercostal muscle pedicle, or internal mammary artery pedicule have all been used to prevent early airway ischemia and to protect against mediastinal dehiscence. Recent reports of bronchial revascularization are very encouraging (54), but this procedure is associated with increased donor and recipient operating time.

The majority of airway complications can be detected by early surveillance bronchoscopy. Airway strictures and segments of bronchomalacia can be successfully managed using periodic dilatation and placement of endobronchial stents in some cases (53,55). The rarely encountered airway dehiscence can be treated by repeated endoscopic debridement and dilatation to maintain airway permeability until a stricture develops. Distal strictures of the main right or left bronchus may involve the upper lobe bronchus. Stenting this type of stricture remains very disappointing.

### B. Cytomegalovirus Infection

Experimental cytomegalovirus pneumonia in animal models and clinical findings in bone marrow transplantation, as in recipients of other solid organs, have

indicated that immunological processes may play a direct role in the genesis of histological and clinical manifestations in CMV pneumonia. In fact, virus reactivation may lead to more or less specific immunoreaction of the host. Subsequently this may cause the picture of histological damage in the transplanted organ. However, the mechanism of this nonspecific lung damage is still an unresolved problem. Among the possible mechanisms, a compelling body of evidence suggests that there is an augmented alloreactivity mediated by cytotoxic or delayed-type hypersensitivity responses to expressed cell surface antigens, which could be products of the viral genome or upregulated native cell-surface antigens. CMV infections can upregulate expression of donor organ MHC class I and II molecules that may be considered alloantigens by immune effector cells of the recipient (56). Humbert et al. (57) demonstrated an increased alveolar perforin and granzyme B gene expression during CMV pneumonia in lung transplant recipients. Perforin is found primarily in cytoplasmic granules derived from cytotoxic T lymphocytes and natural killer cells and is considered an important cytotoxic factor in these cells. Granzyme B is another protein involved in lymphocyte-mediated lysis. This increased gene expression may correspond to an activation of CMV-specific cytotoxic clones and/or to a nonspecific cytotoxic cell activation, which may lead to the acute lung damage observed in these patients.

Prevention of CMV infection after transplantation has been extensively studied, but there are few reports concerning lung transplantation. At the University of Pittsburgh, the introduction in 1986 of seronegative blood products for seronegative recipients receiving seronegative grafts reduced the incidence of CMV infection from 44 to 8%. In our experience no blood transmitted CMV infection occurred in seronegative recipients. Immunization of seronegative candidates may be a means of attenuating the disease due to primary CMV infection. Beneficial results appear to have been obtained by Plotkin et al. (58) with a live attenuated strain of CMV in renal transplant recipients studied in a double-blind, randomized, placebo-controlled trial. However, this vaccine is not yet available. Posttransplant passive immunization has not been studied in lung transplantation. Studies of other types of transplantation have yielded discrepant results. A recent meta-analysis carried out in 18 randomized studies shows lowered incidence of symptomatic CMV infection with no significant difference in patients receiving specific or polyvalent immunoglobulins.

High doses of acyclovir (3.2 g/day for months) in renal transplantation and intravenous ganciclovir (10 mg/kg days 1–15 followed by 6 mg/kg days 15–30) in heart transplantation reduced the incidence of CMV disease in randomized studies. In lung transplantation only nonrandomized and small series have been reported. Different regimens of either high-dose acyclovir or ganciclovir alone or followed by acyclovir failed to prevent CMV pneumonitis. Our experience of prophylactic ganciclovir was also negative. Nineteen high-risk patients received a 15- to 60-day course of ganciclovir as prevention beginning after day 14: this

treatment did not reduce the incidence of symptomatic infection (15/19) or pneumonitis (9/19). However, occurrence of the first episode of infection was significantly delayed (76 + 41 days with ganciclovir prevention versus 33 + 13 days without prevention). Besides cost, prolonged prophylactic regimens may increase the risk of emergence of resistant viral stains, as described in the acquired immunodeficiency syndrome (AIDS).

Matching seronegative recipients with seronegative donors is the safer and less expensive way to avoid CMV infection in this population, as pointed out by the Cambridge group. As in other studies, the proportion of CMV-seronegative donor and recipient was well balanced (D− = 30; R− = 29); thus, one may speculate that CMV-seronegative donors should be reserved for CMV-seronegative recipients without affecting the number of transplantations. This objective, however, needs firmer support from all transplantations teams and precise rules from the appropriate organizations.

### C. Graft Lung Physiology

Lung transplantation results in denervation of the graft below the level of the anastomosis, and accordingly recipients of lung transplants represent an unusual population to investigate the regulation of ventilation, bronchial reactivity, and pattern of breathing during exercise.

#### *Ventilatory Responses during $CO_2$ Rebreathing*

Some studies (59,60) found an approximately 40% reduction in the hypercapnic ventilatory responses of transplant recipients when compared with normal subjects. This depressed response may be due to lower respiratory tract denervation.

#### *Airway Hyperreactivity*

The airways of patients with bilaterally denervated lungs (heart-lung and double lung transplants) were significantly more reactive to metacholine and histamine than the airways of patients with unilaterally denervated lungs (61). This bronchial hyperreactivity is associated with airway inflammation and could reflect denervation hypersensitivity of airway smooth muscle muscarine receptors (38). Morrison et al. (62) demonstrated a correlation between diurnal variations in $FEV_1$ after heart-lung transplantation and airway inflammation.

#### *Mechanical Lung Function*

Glanville et al. (63) demonstrated that the presence of a stable restrictive defect after lung transplantation is determined primarily by the volumetric constraints of the recipient chest cavity and, within these constraints, by the strength and efficiency of the thoracic musculature.

### *Cardiopulmonary Exercise Testing*

Sciurba and coworkers (46) compared the ventilatory response in seven recipients of heart-lung transplants who had normal pulmonary function and seven recipients of heart transplants using an incremental bicycle ergometry. A similar ventilatory response to exercise was found in all recipients (heart and heart-lung). However, in patients with heart-lung transplants (with total denervation of the respiratory system), the increase in ventilation was caused by a more gradual rise in the respiratory rate and a more rapid increase in tidal volume than in those with heart transplants (with intact pulmonary nerves). The authors suggest that the loss of innervation of intrapulmonary receptors may be responsible for this difference in breathing pattern.

Miyoshi and coworkers (64) compared exercise performance in single and double lung transplantation. They found that maximum $VO_2$ was 44.2 and 48.5% of predicted maximal $VO_2$ in single and double lung transplant groups, respectively, with no evidence of ventilatory limitation to exercise in either group. Both single lung and double lung recipients showed a maximum $VO_2$ similar to that of heart-lung recipients.

### *Mucociliary Function*

Impairment of mucociliary function occurs after lung transplantation and may predispose patients to repeated pulmonary infections. This depressed mucociliary function recovers partially during the late postoperative period (2,65), and this recovery is probably due to revascularization rather than to reinnervation.

## D. Obliterative Bronchiolitis

Obliterative bronchiolitis has emerged as the major long-term complication of lung transplantation. It is characterized by an inflammatory process with a particular predilection for the bronchioles of the transplanted lung. This complication is the leading cause of late mortality in lung transplantation. The diagnosis of obliterative bronchiolitis is based on clinical, physiological, and pathological aspects.

The clinical features are an insidious onset of cough with productive sputum and dyspnea. The development or worsening of airflow limitation found in pulmonary function tests usually heralds this complication. In fact, an irreversible decline in $FEV_1$ of more than 20% is usually suggestive of obliterative bronchiolitis. The diagnosis can be confirmed histologically by transbronchial biopsies (sensitivity ranging from 5 to 99%) or open lung biopsy if the diagnosis is in doubt.

Obliterative bronchiolitis may lead rapidly to a severe respiratory failure or may evolve more insidiously with progressive decrements in $FEV_1$. Actually the

prevalence of obliterative bronchiolitis is 20–40% in long-term survivors of lung transplantation, leading to death in up to 50% of these patients.

### *Pathological Features of Obliterative Bronchiolitis*

Autopsy studies and histological material from detransplanted lungs may reveal a classic aspect of obliterative bronchiolitis: obliteration of many bronchiols and vessels with cellular and/or fibrotic tissue. In some cases, however, the pathological pulmonary alterations are more complex with a patchy distribution of airway damage. The inflammatory and reparative process in these cases may extend into the alveolar ducts and alveolar spaces (organizing pneumonia). Other lesions may be observed on the grafts: stenosis of main bronchi, interstitial pneumonia, intimal fibrosis, and focal evidence of acute rejection (15,66).

### *Etiology of Obliterative Bronchiolitis*

Although multiple etiologies have been proposed, recent evidence suggests that chronic pulmonary rejection may be a major determinant of this complication. However, a variety of processes unrelated to transplantation may also cause obliterative bronchiolitis. These include viral and bacterial infections, toxic inhalants, bronchial obstruction, and chronic aspiration. These processes may affect the lung allograft recipient as well as the nontransplanted patient. The Pittsburgh Group (35,67) has demonstrated a definitive association between viral infection and the subsequent development of obliterative bronchiolitis. The mechanism of this association appears to be the upregulation of antigenic molecules in virally infected cells of donor specificity, increasing the susceptibility of the previously tolerated allograft to rejection. Cerrina and coworkers (68) demonstrated that cytomegalovirus mismatch (sero-negative recipient vs. sero-positive donor) was a significant risk factor for obliterative bronchiolitis after heart-lung and double lung transplantation.

### *Animal Models of Obliterative Bronciolitis*

Hertz and coworkers (69) hypothesized that obliterative bronchiolitis results from an alloimmune reaction directed against airway targets. To test this hypothesis, they transplanted murine tracheobronchial grafts into the subcutaneous tissue of immunocompetent recipient animals. Twenty-one days after transplantation, airway inflammation was present in 23 of 24 allografts vs. 2 of 9 isografts. A fibroproliferative process resulting in compromise of the airway lumen by granulated tissue was also observed in 20 of 24 allografts vs. 0 of 9 isografts. This interesting model may be useful to study the pathogenesis and treatment of obliterative bronchiolitis in lung transplantation.

*Prevention and Treatment of Obliterative Bronchiolitis*

Prevention of obliterative bronchiolitis is based on an optimal maintenance of the immunosuppressive drug regimen. A prompt diagnosis and treatment of acute rejections and infections could also influence the evolution of this complication. Careful cytomegalovirus matching between donor and recipient is also recommended.

Treatment of obliterative bronchiolitis requires augmenting the immunosuppressive therapy with high doses of corticosteroids, azathioprine, and antilymphocytic agents. However, in these patients there is an increased risk of infection due to the intensive immunosuppressive therapy. Finally, single lung retransplantation (49,66) represents a therapeutic option in the most severe cases, but the efforts must be directed toward a better prevention of deterioration in lung function.

### E. Choice of Transplant Procedure

Combined heart-lung transplantation was introduced in 1981 at Stanford University for primary pulmonary hypertension (7), and in 1986 the Toronto Transplant Group reported successful single-lung transplantations in two patients with pulmonary fibrosis (70). The successful extension of single lung transplantation to other end-stage lung diseases (71) and the emergence of the bilateral sequential technique for double lung transplantation have diversified the choice of transplant procedures. The question of which procedure should be performed cannot be answered precisely. Low and coworkers (72) compared early morbidity, mortality, and functional results in patients undergoing either single or bilateral lung transplantations for end-stage chronic obstructive pulmonary disease. Both unilateral and bilateral transplantations were successful. Significantly higher values were attained for $FEV_1$ in the bilateral transplantation group; however, comparisons of exercise capacity have shown a less impressive advantage of bilateral over single lung transplantation, while the patients receiving bilateral lung transplants were at greater risk of postoperative complications. Finally, longer follow-up periods are needed to better define the optimal transplantation procedure in these patients.

### F. Posttransplant Lymphoproliferative Disorders

Lymphoproliferative disorders have been reported in solid organ transplantation, in HIV infection, and in patients receiving immunosuppressive treatments. The posttransplant lymphoproliferative disorder is a serious and at times fatal complication of solid organ transplantation. There is an increasing body of evidence that links most cases of posttransplant lymphoproliferative disorder with the Epstein-Barr virus: almost all of these proliferations are of B cell type and are associated

with the presence of the Epstein-Barr virus. Posttransplant immunosuppression allows reactivation of the Epstein-Barr virus infection in seropositive recipients. In the presence of drug-induced defective T-cell surveillance, infected B cells may escape immune recognition, resulting in a proliferative disease. Differences in incidence of posttransplant lymphoproliferative disorders in transplant centers have been reported (0.5–5%), the higher incidence having been noted in patients undergoing heart-lung transplantation (73). In solid organ transplantation, the vast majority of such lesions were extranodal with involvement of the brain, liver, lungs, or graft.

Parameshwar et al. (74) presented the experience of the Papworth Hospital Group (Cambridge) in 137 heart-lung and 31 lung transplants. In these patients immunosuppressive therapy consisted of antithymocyte globulin in the induction phase and a combination of cyclosporine, azathioprine, and prednisolone as maintenance therapy. Rejection episodes were treated with pulse methylprednisolone, and antithymocyte globulin was reserved for refractory episodes. Seven patients (4.2%) developed lymphoproliferative disease between 2 and 18 months after transplantation. In five patients the disease was confined to the transplanted lungs. Epstein-Barr virus serology was positive in four patients (three reactivations and one primary infection a year before a lymphoproliferative disease), negative in two patients, and not available in one patient. Treatment consisted of a reduction in cyclosporine and administration of oral acyclovir. In addition, one patient with invasive disease was treated with chemotherapy. Two of the seven patients died: in both the diagnosis had not been made antemortem. In the remaining four, treatment was successful with clinical and radiological resolution. These results demonstrate that lymphoproliferative disorders are frequent after lung transplantation and that the allograft lung is a common site for these lesions to occur. Response to therapy was frequently successful. The Epstein-Barr virus infection was detected serologically in 66% of the cases, but in situ hybridization was not performed to detect Epstein-Barr virus genomes in any of the patients.

### G. Future Prospects: Xenotransplantation

Interest in xenotransplantation has recently increased dramatically (75), focusing on the "possible" use of discordant xenografts to solve the donor shortage problem. The major barrier to xenotransplantation is hyperacute rejection. Many mechanisms are involved in this rejection, including:

Specific reactions of the recipient's natural antibodies with the donor's antigens
Direct activation of the recipient's complement system by the endothelial cells in the donor's organ
Failure of complement inhibitory proteins in the donor's graft to block activation of the recipient's complement system (76).

Furthermore, the transmission of endogenous retroviruses from xenografts (77) to recipients is a specific problem elicited by xenotransplantation. Further studies are needed to resolve these problems and to find the "optimal" discordant xenografts.

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# 33

# Decision Analysis

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Decision analysis is a discipline designed to assist physicians in the evaluation of a particular intervention under consideration. This quantitative approach of costs and benefits in terms of patient risk, discomfort, or money enables the physician to choose an optimal strategy.

Initially developed for economic purposes in industry in the early 1960s, this methodology has found many applications in health care (1–4). In addition to being a rigorous approach to clinical decision making, decision analysis reinforces the fact that diagnostic procedures must be justified by specific therapeutic or prognostic issues. Decision analysis can also assist in choosing a diagnostic or therapeutic strategy in an environment of limited resources. This of course is dependent upon an open discussion of the inherent ethical issues at play (5–7).

Physicians today are overwhelmed by new sophisticated and expensive diagnostic and therapeutic procedures. The evaluation of a new test or therapy should obviously be the first step before any diffusion of the technique. We shall describe briefly how to estimate the accuracy of a test and how to assess the costs or benefits associated with the introduction of a new procedure in patient management.

## I. How to Assess the Accuracy of a Diagnostic Test

The decision to perform a diagnostic test (8,9) is based on the assumption that the results will significantly change the pretest probability that the disease is present. The physician must be aware of the extent to which the test result would reduce the previous diagnostic uncertainty. Furthermore, he must decide what level of uncertainty warrants further information before therapy can be initiated. In addition, the accuracy of the diagnostic test must be reviewed in order to interpret a positive or negative result in a specific patient.

The first question is which reference procedure, or "gold standard," the new test will be compared to. This reference procedure provides a definition of patients with or without the disease in question. In the case of bacterial pneumonia, the gold standard may be a positive blood culture, but this may be too stringent a criterion. Others have proposed the use of bacterial analysis of bronchoscopic aspirates, yet with this technique samples may be contaminated with bronchial or oral bacteria leading to false-positive results (10). The use of a bronchoscopic protected catheter brush, although quite expensive, can avoid contamination by upper airway secretions (11). Clearly, we do not always have a gold standard immediately available or one totally free from error. Once the gold standard is defined, the problem is to determine the accuracy of a new diagnostic technique in detecting the condition, i.e., being positive in patients who actually have the condition. This proportion of correctly identified patients with the disease is called the *sensitivity* of the test. If a test has high sensitivity, it has a low false-negative rate, i.e., the test does not often give a negative result in patients who have the disease. For example, in patients with community-acquired pneumonia and blood cultures positive for *S. pneumoniae*, sputum culture will identify this bacteria in 45–55% of patients, thereby defining the sensitivity of sputum bacteriology (12,13). Sensitivity can also be defined as the true-positive rate or the probability of a positive test result in patients who have the condition.

The second aspect of accuracy is how well the test correctly identifies patients who do not have the condition. This aspect is called the specificity of the test. If the specificity of a test is high, the test has a low false-positive rate, i.e., the test does not often give a positive result in patients without the disease.

Sensitivity and specificity of a diagnostic procedure are commonly found by selecting a group of patients known to have the disease or condition and another group known not to have the disease or condition and administering the test to both groups. The reference population of patients who do not have the disease should still be patients in whom the diagnostic procedure is justified. Furthermore, the reference population of patients with the disease must be precisely defined. For example, the sensitivity of a tumor marker will be different in patients with advanced metastatic cancer compared to patients having a small asymptomatic tumor. Likewise, the specificity of the test should be assessed in patients with a suspected diagnosis of cancer and not in healthy individuals.

As an example, nosocomial pneumonia is a common and life-threatening problem complicating the management of patients requiring mechanical ventilation (14). Abundant literature deals with the accuracy of the procedures used to assess the presence of bronchopneumonia in such patients (11,15–21). There remains, however, considerable controversy about which test should be used—protected specimen brush technique or bronchoalveolar lavage (BAL)—the significance of antibiotic treatment at the time of sampling, and the definition of the gold standard. Many studies have evaluated the protected brush specimen technique in critically ill patients using either clinical criteria or lung specimens obtained from postmortem lung biopsies as a gold standard (11,22,23). With this technique, sensitivity for the diagnosis of nosocomial pneumonia is around 90% with a 95% specificity (20). However, these values are the result of a meta-analysis that does not reflect the heterogeneity of the studies. For example, concurrent antibiotic treatment clearly decreases sensitivity (22,24). Studies on the usefulness of BAL in the diagnosis of nosocomial pneumonia in mechanically ventilated patients are also controversial (16,19–21,25). In a study assessing the usefulness of the protected BAL technique, the gold standard was the histological and bacteriological study of a surgical pneumonectomy performed at the bedside within 30 minutes after death (19). In this circumstance, using a semiquantitative bacteriological analysis, the protected BAL technique identified 77% of causative microorganisms responsible for nosocomial pneumonia with a sensitivity and specificity of 70 and 69%, respectively. This study outlines the fact that some patients with moderate or severe pneumonia had sterile lungs, likely due to the role of antibiotics, thereby explaining the false-negative results of BAL. On the other hand, 10 out of 40 patients whose lungs were positive when cultured but did not have evidence of alveolar infection had histological lesions of bronchiolitis. BAL was negative in two of these patients. Therefore, from this study, it appears that "false-negative" protected BAL is related to "true" sterilized bronchopneumonia in most cases and that "false-positive" protected mini-BAL is often related to bronchiolitis. These results emphasize that the accuracy of a test is highly dependent on the aim of the study, i.e., diagnosis of nosocomial pneumonia versus identification of bacteria requiring antibiotic treatment. The results of this study were similar to those obtained in an experimental model in the baboon (26).

The significance of clinical factors predictive of short-term survival among chronic respiratory insufficiency patients may also be expressed in terms of sensitivity and specificity. In the ICU, illness severity is difficult to evaluate and to correlate with outcome (27). This explains why many scoring systems have been proposed. The Acute Physiology and Chronic Health Evaluation (APACHE) system was the first to be widely validated (28). Simplification led to APACHE II and the Simplified Acute Physiology Score (SAPS), both of which were subsequently validated (29,30). Portier et al. performed a multivariate analysis of 322 patients with chronic respiratory insufficiency admitted to an ICU for acute respiratory failure (31). Several factors were identified as independently predic-

tive due to significant differences in the distribution of these factors for patients who did or did not survive ($p < 0.05$). When compared to the $p$-value, often more information can be drawn from an analysis of the sensitivity and specificity of a particular factor in identifying the condition or outcome. For example, in the study by Portier et al., the death rate was significantly higher in patients with cachexia (27%) than in patients without cachexia (10%) ($p < 0.01$). Data can be presented in a different way, as in Table 1, which shows that 20% of survivors have cachexia and that fewer than 50% of patients who died were cachectic. Clearly, despite a statistically significant difference, the presence of cachexia is not very helpful in predicting short-term survival in the population studied. Another advantage of this approach is that sensitivity and specificity are independent of the prevalence of the disease or condition.

Another way to express the operating characteristics of a test is to use likelihood ratios. The likelihood ratio expresses the odds that the test result occurs in patients with the disease versus those without the disease. Thus, there is one likelihood ratio for a positive test (LR+) and another for a negative test (LR−). LR+ is the odds of a positive test in patients with the disease (sensitivity) versus a positive test in patients without the disease (false-positive rate). A test with a likelihood ratio of 1.0 does not provide any information, since the rates of true positive and false positive are equal. Absolute certainty is obtained for a negative result when the LR− of the test is zero and for a positive test when the LR+ of the test is infinite.

$$\text{LR}+ = \frac{\text{Sensitivity}}{\text{False-positive rate}}$$

$$\text{LR}- = \frac{\text{False-negative rate}}{\text{Specificity}}$$

Therefore, in the prediction of death, the likelihood ratio (LR+) for cachexia is 2.2 (0.44/0.20) and the likelihood ratio for the absence of cachexia (LR−) is 0.67

**Table 1** Calculation of Sensitivity and Specificity of Cachexia for Predicting Immediate Death in Patients with Chronic Respiratory Insufficiency Admitted for Acute Respiratory Failure

| | Death | Survival | Total |
|---|---|---|---|
| Cachexia | 20 | 55 | 74 |
| No cachexia | 25 | 223 | 248 |
| Total | 45 | 278 | 322 |
| | Sensitivity = 20/45 | Specificity = 223/278 | |
| | 0.44 | 0.80 | |

*Source*: Adapted from Ref. 31.

(0.54/0.8). In the same paper, Portier et al. studied a quantitative parameter, the SAPS, and found that the mean SAPS on day 1 was higher in the group of patients who died (SAPS = 13.02 ± 4.3; $n$ = 45) than in the group of surviving patients (SAPS = 11.64 3.9; $n$ = 277) with a $p$-value < 0.05. As with many other tests, SAPS values are measured on a numerical scale. When test values are measured on a continuum, sensitivity and specificity will depend on where the cut-off between a positive test and a negative test is set. This can be illustrated by two hypothetical distributions, assumed to be gaussian, of SAPS values (Fig. 1). The placement of a cut-off point results in the incorrect classification of patients who died with a "negative" SAPS and of patients who survived with a "positive" SAPS. Each cut-off value defines a different sensitivity and specificity.

A useful way to display the relationship between sensitivity and specificity for tests that have continuous outcomes is with receiver operating characteristic (ROC) curves. ROC curves were developed as a way to display signal-to-noise ratios. If one considers true positives to be the "correct signal" from a diagnostic test and false positives to be the "noise," the concept is easily applied. The ROC curve is a plot of the sensitivity (or the true-positive rate) against the false-positive rate (Fig. 2). The identity line (diagonal dotted line) signifies a test that may be positive or negative at random. The closer a ROC curve is to the upper left-hand corner of the graph, the more accurate the test is, because the true-positive rate approximates 1 and the false-positive rate approximates 0. The effectiveness of the test can then be determined by measuring the area between the curve and the identity line. The solid line in Figure 2 illustrates the data obtained in the study of Portier et al. (31). The sensitivity—percentage of dying patients with an index value above a specific cut-off—and the specificity—percentage of surviving patients with an index value below the same specific cut-off—were calculated for

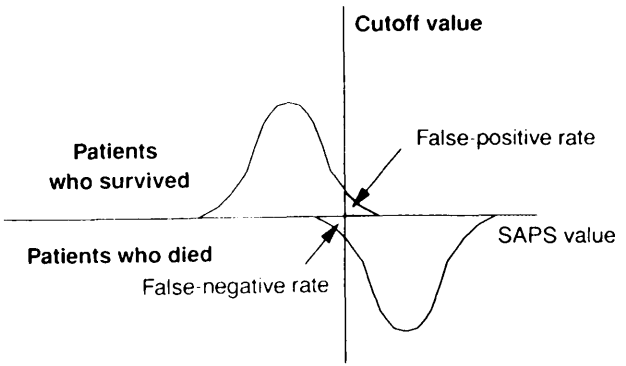


**Figure 1** Effect of the cut-off value on sensitivity and specificity of a test using a quantitative variable.

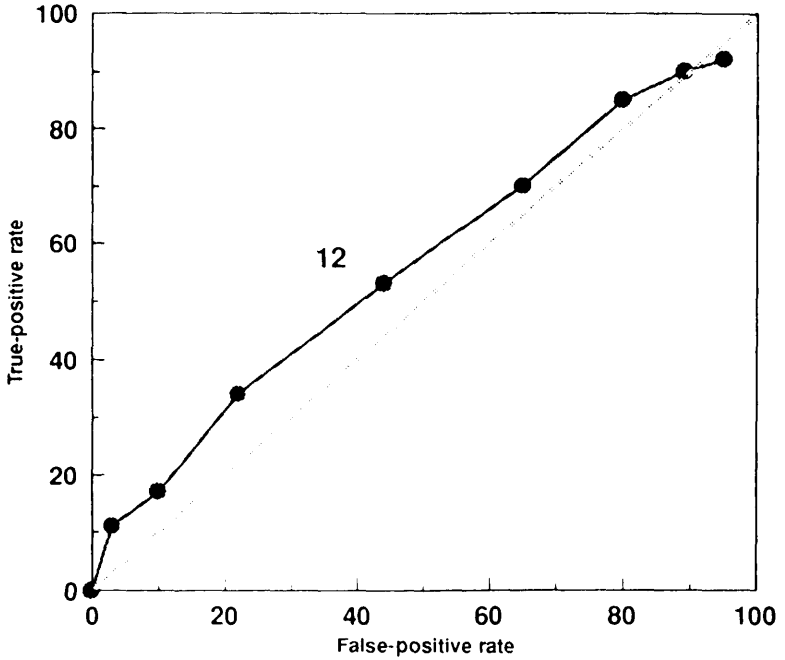


**Figure 2** ROC curve of SAPS score for predicting immediate survival in patients with chronic respiratory insufficiency admitted for acute respiratory failure. (Adapted from Ref. 31.)

each value of the index. This ROC curve is very flat and close to the diagonal, meaning that this index is not useful in predicting immediate survival in the population studied and that a scoring system specific to the population should be developed.

ROC curves can be a useful graphic means for comparing two diagnostic tests or the discriminative value of the same test applied to two different populations without arbitrarily fixing the threshold value. Figure 3 illustrates the comparison of the SAPS system applied to acute respiratory failure in patients with chronic respiratory insufficiency (31) and to a general population of 679 ICU patients (30). A statistical test could have been performed to assess whether these two ROC curves are significantly different. The procedure involves calculation of the area under each ROC curve and uses a modification of the Wilcoxon rank-sum test (32).

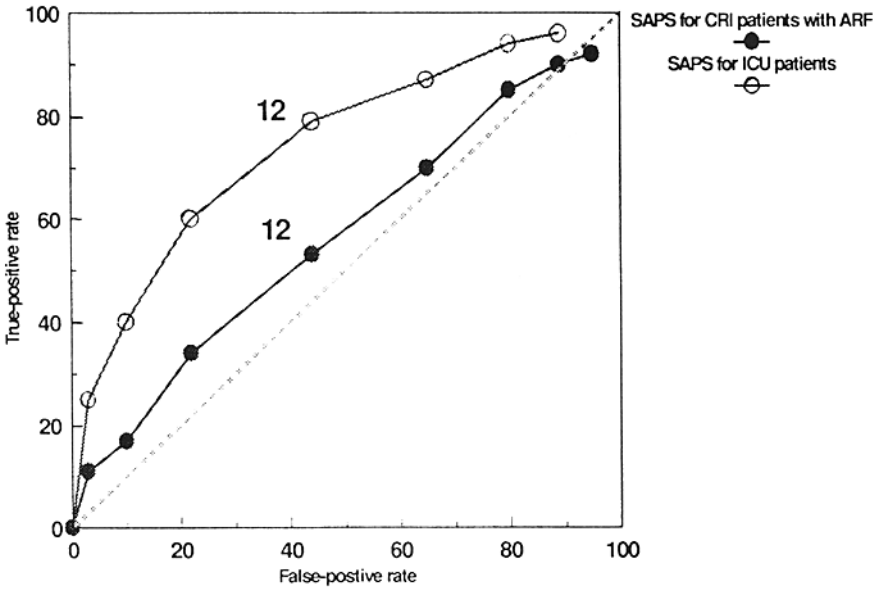


**Figure 3** Comparison of ROC curves of SAPS scores in two populations of patients. See text for explanations. (Adapted from Ref. 31.)

### II. Bayes' Theorem

Unfortunately, sensitivity and specificity cannot be used alone when assessing the value of a diagnostic test in a specific patient. Instead they must be combined with the physician's index of suspicion (or the prior probability) that the patient has the disease. This enables one to determine the probability of disease (or nondisease) once the test result is known. This index of suspicion cannot always be based on probability learned through experiments or observations and sometimes is simply a "best guess." This estimate often begins with baseline prevalence and then is revised upward (or downward) depending on clinical signs and symptoms. Some vagueness is acceptable in the initial estimate of the index of suspicion. The manipulation of prior probability may be easy for some physicians; others may have more difficulty with this concept.

By way of an example, we can discuss the interpretation of the ventilation/perfusion scan in the diagnosis of pulmonary embolism. In the PIOPED study the sensitivity and specificity of lung scintigraphy were evaluated using pulmonary angiography as the gold standard (33). Scans were independently interpreted with chest roentgenograms by two readers and were classified according to pre-established criteria into four categories: high, intermediate, low, and very low

probability. Angiograms were interpreted with lung scans as having acute pulmonary embolism present, absent, or uncertain (Table 2).

Suppose one has a patient with a history of deep venous thrombosis complaining of a recent shortness of breath with normal chest x-ray. The clinical assessment of the probability of pulmonary embolism is thought to be 0.5 (50%). The lung scan is interpreted as high probability. In this patient, with a prior clinical probability of pulmonary embolism of 50%, how will a high probability result of a lung scan that is 41% sensitive and 97% specific for pulmonary embolism (33) change the probability of disease or nondisease? These new probabilities are known as the predictive values or the posterior (posttest) probabilities. The chance that a patient with a positive test has the disease is the ratio of true positive subjects to all positive subjects (the sum of true and false positives). This ratio can be rewritten in terms of sensitivity and specificity. The probability of being a true positive is the product of the probability of having the disease (prior probability) and the probability of having a positive result (sensitivity). Similarly the probability of being a false positive is the product of the probability of not having the disease (1 − prior probability) and the probability of having a positive result in this condition (1 − specificity).

$$\text{Posterior probability} = \frac{\text{True positive}}{\text{True positive} + \text{False positive}}$$

$$= \frac{\text{Prior prob} \times \text{Sensitivity}}{(\text{Prior prob} \times \text{Sensitivity}) + (1 - \text{Prior prob}) \times (1 - \text{Specificity})}$$

**Table 2** Sensitivity and Specificity of Various Patterns of Lung Scan for Diagnosis of Pulmonary Embolism

| Scan category | Pulmonary embolism present | Pulmonary embolism absent |
|---|---|---|
| High probability | 102 | 14 |
| Intermediate probability | 105 | 217 |
| Low probability | 39 | 199 |
| Near normal/Normal | 5 | 50 |
| Total | 251 | 480 |

| Scan category | Sensitivity (%) | Specificity (%) |
|---|---|---|
| High probability | 41 | 97 |
| High or intermediate probability | 82 | 52 |
| High, intermediate, or low probability | 98 | 10 |

*Source*: Ref. 33.

This formula derived from Bayes' theorem, is used to revise the prior probability of pulmonary embolism and gives the following posterior probability:

$$\text{P Emboli/High probability scan} = \frac{0.5 \times 0.41}{(0.5 \times 0.41) \times (1 - 0.5) \times (1 - 0.97)}$$
$$= 0.93$$

The relationship between prior and posterior probabilities can be graphically illustrated. Figure 4 shows how the posterior probability or the positive predictive value varies compared with prior probabilities as a function of high, high or intermediate, and low probability lung scans. The identity line signifies that test result would not change the prior probability. This figure shows that a high-probability lung scan is useful in confirming pulmonary embolism when prior probability is intermediate. An intermediate pattern of scintigraphy does not provide diagnostic information. On the same graph, the negative predictive value or the posterior probability of pulmonary embolism is illustrated in the setting of a low-probability scan. It becomes evident that a low-probability lung scan does not rule out the diagnosis of pulmonary embolism regardless of the prior probability.

The level of prior probability is an important factor when interpreting the result of a test. The lower the prior probability, the more likely a positive test will be a false positive. For example, let us assume that the prior probability is 0.05 and that the lung scan will give a high-probability pattern. the posterior probability is 0.42, meaning that there are 6 chances out of 10 (0.58) that the result is a false

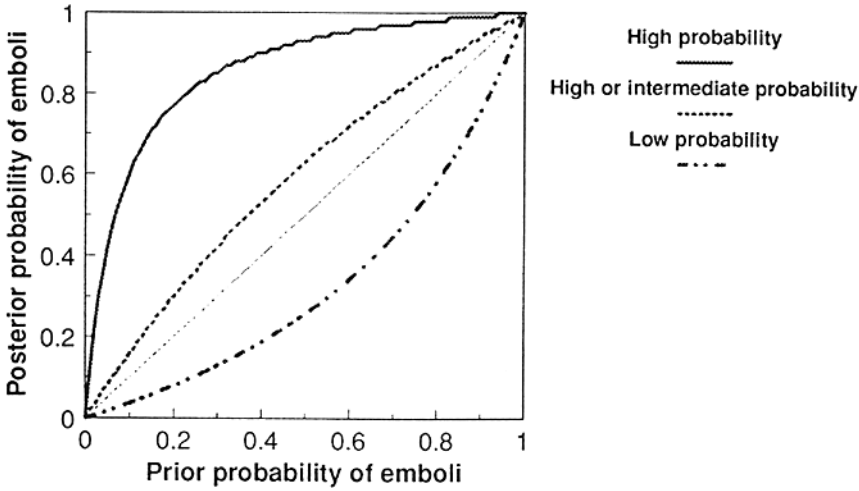


**Figure 4** Bayes' theorem: relationship between prior probability and posterior probability for various patterns of lung scan in the diagnosis of pulmonary embolism.

positive. This is a particularly relevant consideration in tests screening for a rare disease.

Another method for revising prior probabilities uses the likelihood ratio and works with prior odds instead of prior probabilities. The likelihood ratio for a positive test is multiplied by the prior or pretest odds to obtain the posttest odds of a positive test. In the case we studied above, the likelihood ratio of a high-probability scan is LR+ = Sensitivity/False-positive rate = 0.41/(1 − 0.97) = 0.41/0.03 = 13.7. Before using the likelihood ratio, we must convert the prior probability into pretest odds. If the prior probability of pulmonary embolism before the lung scan is 0.5, then the pretest odds are found by dividing the prior probability by one minus the prior probability:

$$\text{Pretest odds} = \frac{\text{Prior probability}}{1 - \text{Prior probability}}$$

In our example, pretest odds = 0.5/(1 − 0.5) = 1. Combining the pretest odds with the likelihood ratio, we obtain the posttest odds: 1 × 13.7 = 13.7. These odds can then be reconverted to a posterior probability, the predictive value of a positive test, by dividing the odds by one plus the odds.

$$\text{Posterior probability} = \frac{\text{Posttest odds}}{1 + \text{Posttest odds}}$$

Posterior probability becomes 13.7/(1 + 13.7) = 0.93. Of course this probability is the same result we found with the previous method. A nomogram published by Fagan renders the likelihood ratio approach simpler to use (34).

An advantage to the use of odds with the likelihood ratio is the possibility of combining the results of various independent tests while taking into account the positive or negative results of the tests. Let us go back to the diagnosis of nosocomial pneumonia in mechanically ventilated patients. In a prospective study by Torres et al (35), the authors selected by logistic regression analysis five factors independently associated with a higher risk of nosocomial pneumonia during mechanical ventilation.

Table 3 shows the likelihood ratios associated with the presence (LR+) and absence (LR−) of each factor. In this population the overall prevalence of nosocomial pneumonia was 0.25. A patient admitted to the ICU will therefore have a prior probability of acquiring nosocomial pneumonia of 0.25, or pretest odds of 0.25/(1 − 0.25) = 0.33. Let us take as an example a patient suffering from COPD who has been reintubated and requires positive end expiratory pressure (PEEP) but has no other risk factors. The posttest odds are the product of pretest odds and the LR+ for COPD, reintubation, and PEEP multiplied by the LR− of the factors not present: 0.33 × 1.23 × 4.55 × 1.53 × 0.71 × 0.81 = 1.63. The reconversion to probability gives a predictive value of 0.65. This high risk of

**Table 3** Likelihood Ratios of Independent Variables for the Diagnosis of Nosocomial Pneumonia in Mechnically Ventilated Patients

| Variable | LR+ | LR− |
|---|---|---|
| Reintubation > 1 | 4.55 | 0.67 |
| Gastric aspiration | 4.1 | 0.81 |
| MV duration > 3 days | 0.78 | 0.71 |
| COPD present | 1.23 | 0.83 |
| PEEP present | 1.53 | 0.87 |

LR, Likelihood ratio; MV, mechanically ventilated.
*Source*: Ref. 35.

nosocomial pneumonia may justify, after analysis of clinical and radiological data, the use of a protected brush specimen technique or of protected BAL to confirm the diagnosis and to identify the bacteria involved. The powerful feature of this approach is that it includes information provided by positive as well as negative results of a test. However, an important assumption is the absence of redundant information in the various tests used. We are assuming that the tests are independent, which is usually not true. A low-probability threshold justifying a clinical decision and the use of a limited number of tests (less than 5) chosen after logistic regression may prevent this bias.

## III. Clinical Application of Decision Analysis

Determining the characteristics of a test and interpreting the results by revising the prior probability of disease must be integrated in a diagnostic and/or therapeutic strategy. The physician is often confronted by several possible diagnostic tests or therapeutic choices, each with its own potential value and its own attendant risks. Decision analysis provides a mechanism for describing complex clinical problems explicitly. It aids in identifying available courses of action, assessing the probability and value of all possible outcomes, and in making a simple calculation to select the optimal choice.

The first stage is to define the problem. A decision tree illustrating how to decide whether or not to perform a pulmonary arteriogram in a patient with a suspected pulmonary embolism is shown in Figure 5. Considerations are limited to a small set of important choices and possible outcomes. The tree contains decision and chance nodes. Decision nodes are shown as squares and represent the point at which the clinician must make a choice. For example, the first decision

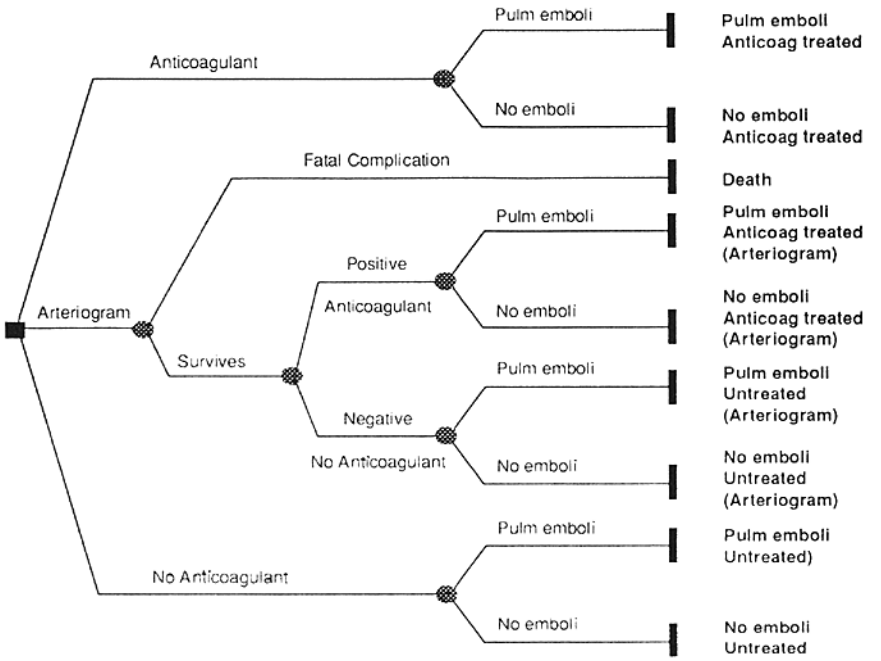


**Figure 5** Decision tree used to decide whether or not to perform a pulmonary arteriogram in a patient with a suspected pulmonary embolism.

node confronts the clinician with the choice of pulmonary arteriogram, anticoagulant treatment, or no treatment. Chance nodes are denoted by circles and represent possible outcomes outside the control of the clinician. For example, the outcome of angiogram may be death or survival of the patient. At the end of each branch is a termination node (rectangle), which represents the outcome of the branch.

This decision tree could be applied to the following clinical problem: a 60-year-old man with known mitral stenosis, severe COPD ($FEV_1$: 40% of predicted), and a history of duodenal ulcer is admitted to the ICU for acute respiratory failure. On the day of admission the sputum is purulent and contains some blood. The patient complains of a right-sided pleural chest pain. On examination, right pleural friction rubs and diffuse bronchial rales are noted. There is no clinical sign of deep venous thrombosis, but peripheral noninflammatory edema is present. Chest x-ray shows hyperinflation with a centro-lobular emphysema pattern, vascular redistribution, and some patchy alveolar opacities in the right lower lobe. EKG and echocardiography suggest right heart hypertrophy and an increased left

auricular size. Room air arterial blood gas reveals hypoxemia ($Po_2$ = 40 mmHg) with hypercapnia ($Pco_2$ = 45 mmHg), slightly less than a previous baseline value ($Pco_2$ = 50 mmHg). After furosemide-induced diuresis, a bedside catheterization of the pulmonary artery is performed, revealing a pulmonary pressure of 65/35 and a pulmonary capillary wedge pressure of 20 mmHg. The diagnosis of pulmonary embolism is considered and heparin therapy begun. One week later the patient becomes less unstable and consideration is given to confirming the diagnosis of pulmonary embolism. A lung scan is performed but proves noncontributive due to the severity of the COPD (36). The risk of carrying out a pulmonary angiogram must now be weighed, particularly considering the increased risk of bleeding with long-term anticoagulation.

The next stage in the decision analysis process is to fill in the probabilities and utilities of each outcome. Probabilities can be obtained from data collected in similar patients, from case material in the literature, or from the estimates of an expert. However, since the patient under consideration is often not a typical case, the probability may only be the "best guess" of the physician adapting data from the literature. In our example, based on the clinical setting, the probability of a pulmonary embolism can be estimated to be 0.6. This probability is also known as the prior probability Selecting a value for the mortality rate of pulmonary angiogram in this patient is difficult. While in the literature the risk is estimated at 0.4% (37), in this patient, because of persistent pulmonary hypertension, the mortality rate was taken to be 1.0%. The expected sensitivity of the angiogram is decreased to 0.7 since a numerical angiograph was used and at one week some resolution of the emboli can be expected. The severe COPD may account for anatomical changes responsible for false-positive results, and the specificity was taken to be 0.95 (37).

The next step is to assign a probability to each branch of chance nodes. For example, the chance of a fatal complication is 1% for angiography. The probability of a positive result of the angiogram is the sum of the probabilities of being a true (prior probability × sensitivity) or a false positive (1 − prior probability × 1 − specificity), calculated to be 0.44. The probability of a negative result is the complementary probability, 0.56. We then use Bayes' theorem to find the revised probability of having a pulmonary embolism, given a positive angiogram. This probability is the probability of being a true positive (prior probability × sensitivity) divided by the probability of having a positive angiogram, 0.95.

In order to evaluate each of these potential outcomes, we must first decide what the reference point of these value assessments should be: the patient, the physician, or society. Usually the physician attempts to optimize the outcome for the patient and disregards the consequences to society. In this perspective, utility can be measured in various terms, such as life expectancy, 5-year survival, or quality-adjusted life expectancy but should integrate as much as possible the values of the patient. Methodology has been developed to approach patients with a

series of questions designed to help them assess each potential outcome (38–40). In our pulmonary embolism example, the value judgments regarding mortality were made without the input of the patient. For each outcome, life expectancy was calculated. These calculations involve many assumptions and are only rough estimates of the situation.

In Table 4, the mortality-related values (utility) are numerically estimated and adjusted on a scale of 0 to 100. Annual rates of mortality are used because it is possible to combine the effect of several influences simply by adding the respective excess rates to the baseline rates (41,42). Furthermore, life expectancy can be calculated by taking the reciprocal of the combined rates. The annual mortality rate for 60-year-old white males is estimated to be 16.8/1000 (43). The excess mortality rate associated with valvular heart disease and atrial fibrillation, excluding embolic events, is approximately 12/1000/yr (41). The excess mortality rate due to COPD with an $FEV_1$ of 45% and a history of pulmonary hypertension is estimated to be 239/1000/yr (44). Thus, the total baseline mortality for this patient is calculated to be 16.8 + 12 + 239, or 268/1000/yr.

The mortality for heparin-treated pulmonary emboli is approximately 50/1000/yr (37). Treatment is thought to reduce the mortality rate by 75% (45). The excess mortality rate for anticoagulant therapy is a clinical estimate and integrates the known rates of bleeding approximated at 5% (46,47). The probability and utility values for the case example are summarized in Figure 6.

The next step is to combine the probability of each outcome with the utility of that outcome and thereby calculate an expected utility for each node in the tree. For the "no-anticoagulant" option, the expected utility of the upper branch is $0.60 \times 57$, or 34.2, and of the lower branch $0.40 \times 100$, or 40. Therefore, the utility

**Table 4** Calculations of Utilities Using Mortality Rates

| Outcomes | Mortality (total rate) | Expected survival (yr) | Utility (× 26.8) |
|---|---|---|---|
| No emboli untreated | 268 | 3.73 | 100 |
| No emboli treated | 268 + 50 | 3.14 | 84 |
| Pulmonary emboli treated | 268 + 50 + 50 | 2.71 | 72 |
| Pulmonary emboli untreated | 268 + 200 | 2.13 | 57 |
| Death after arteriogram | 0 | 0 | 0 |

| Conditions | Estimated annual mortality rate (per 1000 patients/yr) |
|---|---|
| Baseline state of patient | 268 |
| Excess for pulmonary emboli untreated | 200 |
| Excess for pulmonary emboli treated | 50 |
| Excess for anticoagulation | 50 |

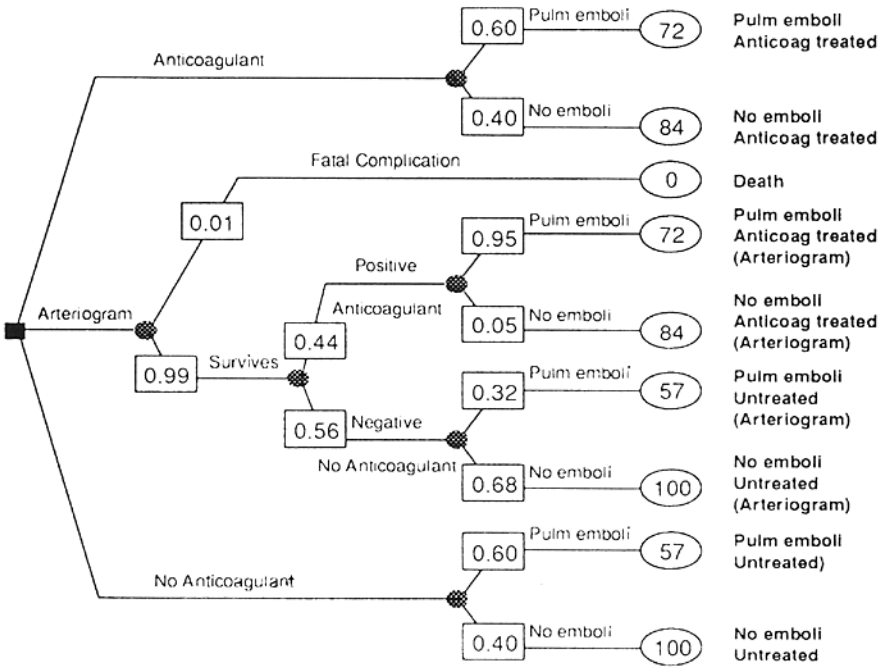


**Figure 6** Attribution of utilities and probabilities to the decision tree. See text for explanations.

of this option is 74.2. The expected utilities of the other chance nodes were calculated in the same way, proceeding from right to left. This resulted in an expected utility of 76.8 for anticoagulant therapy without angiogram and 79.4 for the choice of performing pulmonary angiography. The option with the highest expected utility corresponds to the choice that, on average, will produce the most optimal outcome. In this example, the optimal decision is therefore to perform a pulmonary arteriogram.

Finally, it is important to examine the impact on the decision of possible data errors. Sensitivity analysis is a tool to assess which data parameters can be expected to affect the decision. This permits a determination of how robust a particular decision is. The identification of data to which the decision is sensitive can also be a stimulus for new clinical research. Software are available enabling personal computers to easily perform this task (48,49). In the clinical problem we described, we often had to rely on assumptions concerning the prior probability of emboli as well as complication rates for anticoagulant therapy and pulmonary angiogram. We can now analyze the impact of some of these assumptions on the decision. Figure 7 shows values for the expected utility of each of the tree choices

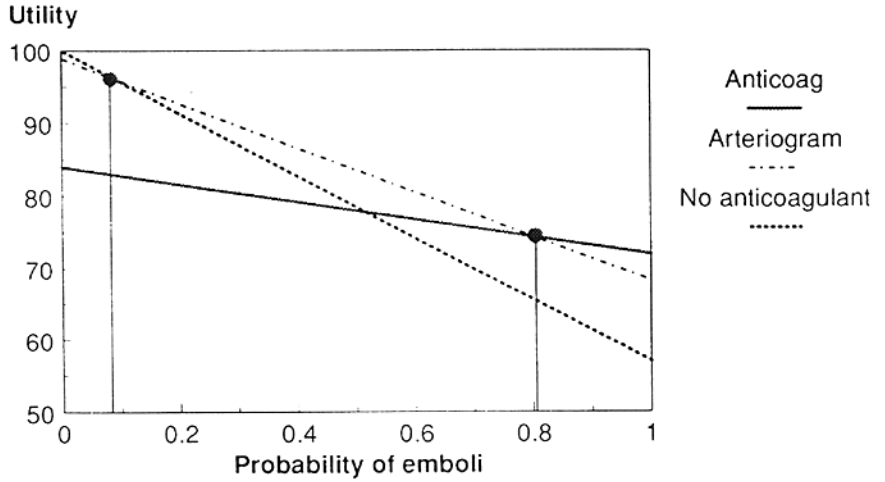


**Figure 7** Sensitivity analysis: effect of the probability of pulmonary embolism on the expected utility of each strategy.

as a function of prior probability. The optimal choice for any prior probability of pulmonary emboli will be the one with the highest utility. There are three intersections between the lines, each of which corresponds to a threshold probability. The two dots in Figure 7 correspond to the thresholds between which the optimal decision is to perform pulmonary angiography. The lower threshold is 0.15 and signifies that point where there is an equivalent benefit to stopping anticoagulant therapy or to performing angiography. The upper threshold is defined as the interaction of the expected utility of performing angiography with that of continuing anticoagulant therapy (0.73). Our initial estimate of the prior probability lies between both thresholds. Therefore, the decision remains valid despite some error in this estimate.

A similar analysis can be conducted for the risk of pulmonary angiography, initially estimated to be 0.01. Recalculation of utilities with variable risks between 0 and 0.05 shows a mortality threshold of 0.042. This means that for a prior probability of 0.6 and a mortality rate higher than 0.042, the optimal decision is to continue anticoagulant therapy without carrying out angiography.

Finally, Figure 8 shows the effect of mortality rate due to anticoagulation therapy on the utility of each type of decision. Below a mortality rate of 34/1000/yr, the optimal choice, given a prior probability of 0.6, is to continue anticoagulation. A higher rate favors performing a pulmonary angiogram. Therefore, the decision is sensitive to the mortality rate of anticoagulation therapy and should lead to a more precise study of this risk in the patient under consideration.

This decision tree may appear incomplete or truncated. We could have

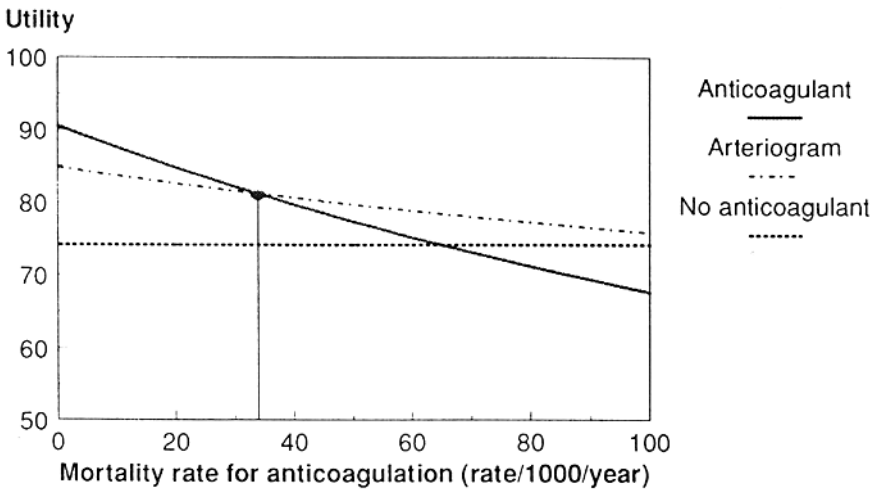


**Figure 8** Sensitivity analysis: effect of the mortality rate of anticoagulant therapy on the expected utility of each strategy.

extended the tree further to the right. However, each outcome may be seen as a summary of each potential outcome of the branch described. Many examples of more complete decision trees have been published (50,51). The tree we described here was adapted from a paper by Pauker and Kassirer (52). In this publication, the authors showed how morbidity can be included in the calculation of expected utilities. Various methods have been used to assess utilities. Besides values for life expectancy, techniques have been developed to factor in parameters such as quality of life, monetary values, freedom of disability, and the view of the patient (39,40,53,54). The choice of utility values raises interesting and difficult philosophical issues for decision making (5). These issues confront us whether we use an explicit method for decision making, such as decision analysis, or rely on our clinical perception compiled from experience. The methods of decision analysis can change the way we think (55). Various chapters of this book may raise questions that can be answered using decision analysis. We hope that this article will inspire physicians to apply decision analysis to the numerous topics dealing with acute respiratory failure as well as to other fields of their practice.

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# AUTHOR INDEX

*Italic numbers give the page on which the complete reference is listed.*

## B

## C

## D

## E

## F

## G

## H

## I



## J

## K

## L

## M

## N

## O

## P

## Q



## R

## S

## T

## U



## V

## W

## X



## Y

## Z

# SUBJECT INDEX

## A

## B

## C

## D

## E

## F



## G



## H

## I



## J



## K



## L

## M

## N

## O

## P

## Q

## R

## S

## T

## U



## V

## W

## X