Introduction:

Mechanisms of COPD*

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(CHEST 2000; 117:219S)

The first Aspen Lung Conference entitled “Symposium on Emphysema and the Chronic Bronchitis Syndrome,” was held in 1958. It’s purpose was to develop an understanding of what these terms meant and to begin to unravel the causes and factors associated with the prognosis. The original Aspen Emphysema Conferences were funded by contracts from a branch of the United States Public Health Service. The 8th Aspen Emphysema Conference was held in 1965. It focused on therapy, and chronic bronchitis and emphysema were redefined. Surgery for emphysema was briefly considered. Oxygen therapy was introduced as a possible solution for selected patients with advanced stages of COPD. Principles of home care and pulmonary rehabilitation were introduced. The next three Aspen Emphysema Conferences were on contemporary research in COPD and related disorders.

Beginning with the 12th, these conferences have been supported by donations from industry and from private individuals. The 13th conference was the first to be published as a special supplement in CHEST, and this has been the tradition from that time onward. On the 16th conference was on acute lung injury and ARDS. At that time, the conference’s name was changed to the Aspen Lung Conference. The most common themes of the previous conferences have been COPD, the pulmonary circulation, asthma, and ARDS. A variety of more basic topics, including the relationship between the environment and the lung and the basic science of the lung, have also been covered.

The 26th conference again dealt with COPD and helped us further understand the pathophysiology, structure, and function of disorders characterized by chronic progressive airflow obstruction. It has now been 16 years since COPD was the theme, and most attendees considered this an inordinately long hiatus in view of the explosion of knowledge based upon multidisciplinary research that is gaining momentum.

This year’s conference was on the “Mechanisms of COPD.” Understanding mechanisms of disease forms the foundation for new therapies. This supplement contains state-of-the-art reviews, as well as abstracts of reports that were presented after the state-of-the-art presentations or in the poster sessions. In some cases, slightly expanded mini-papers are included. A special commentary by Professor N. G. M. Orie, MD, about the Dutch hypothesis and the masterful summary by Robert Senior, MD, will be appreciated by all who read this supplement. We hope the readers share some of the thrill that we felt as we attended the 42nd Aspen Lung Conference.

We thank the Francis Families Foundation for their support of the Annual Parker B. Francis Lectureship. We greatly appreciate the generous support of all the sponsors of this year’s conference, and we thank Mrs. Jeanne Cleary for her tireless work, which again made this conference a huge success.

Expiratory Flow Limitation*

Detection and Clinical Implications

Roger S. Mitchell Lecture

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(CHEST 2000; 117:219S–223S)

Abbreviations: FL = flow limitation; NEP = negative expiratory pressure; VT = tidal volume; V-V = tidal expiratory flow-volume

The highest pulmonary ventilation that a subject can achieve is ultimately limited by the highest flow rates that can be generated. Most normal subjects do not exhibit expiratory flow limitation (FL) even during maximal exercise. In contrast, patients with COPD may exhibit FL even at rest, as first suggested by Hyatt.1 This was based on his

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observation that patients with severe COPD often breathe tidally along their maximal expiratory flow-volume curve. The presence of expiratory FL during tidal breathing promotes dynamic pulmonary hyperinflation, with concomitant increase of inspiratory work, impairment of inspiratory muscle function, and adverse effects on hemodynamics. This, together with flow-limiting dynamic compression during tidal breathing, may contribute to dyspnea.

Conventionally, FL is assessed by comparison of the tidal expiratory flow-volume (V˙-V) curves with the corresponding maximal expiratory flow-volume curves: patients in whom, at comparable lung volumes, tidal flows are similar or higher than those obtained during the FVC maneuver are considered flow limited. As discussed below, this approach has both theoretical and practical limitations. Nevertheless, this analysis has been the kernel for understanding respiratory dynamics. Furthermore, it still is commonly used in clinical practice to assess tidal expiratory FL. Accordingly it is useful to review it in some detail.

Figure 1 depicts the V˙-V loops at rest and during maximal exercise, together with the corresponding maximal V˙-V curves of a normal subject and a patient with severe airway obstruction. In the normal subject, even during maximal exercise, the flows are less than maximal (ie, there is no FL). In this case, the increase of tidal volume (V_t) during exercise occurs as a result of both an increase in end-inspiratory and a decrease in end-expiratory lung volume, and the work of breathing during exercise is sustained by activity of both inspiratory and expiratory muscles. In contrast, in patients with airway obstruction, maximal expiratory flows may be attained even at rest. Thus, their increase in V_t during exercise can only occur as a result of an increase in end-inspiratory volume. Furthermore, as a result of excessive expansion of the chest wall, the inspiratory muscles work inefficiently.

With severe dynamic hyperinflation, this phenomenon becomes self-limiting because the changes in volume and inspiratory flow require too high force development by the inspiratory muscles. Thus, in patients with severe airway obstruction, inspiratory muscle fatigue may limit exercise performance. This explains why detection of tidal expiratory FL is of great clinical importance.

However, the conventional approach for detecting expiratory FL, which is illustrated in Figure 1, has an important practical limitation because, as a result of thoracic gas compression during the FVC maneuver, the...
tidal and maximal V˙-V curves have to be measured with a body plethysmograph.\(^8\) This implies that such measurements are usually confined to resting breathing in sitting position. Apart from this, there are several other factors that make assessment of FL based on comparison of tidal and maximal V˙-V curves problematic: (1) volume-dependent changes in airway resistance and lung recoil during the maximal inspiration prior to the FVC maneuver; and (2) time-dependent viscoelastic behavior of pulmonary tissues and time-dependent lung emptying due to time constant inequality.\(^9\)–\(^11\) These mechanisms imply that the maximal flows that can be reached during expiration depend on the volume and time history of the preceding inspiration. Furthermore, since axiomatically the previous volume and time history vary between tidal and maximal inspiration, assessment of FL based on comparison of tidal and maximal V˙-V curves often leads to erroneous conclusions, even if the measurements are made with body plethysmography.\(^12\),\(^13\) Recently, however, an alternate technique, the negative expiratory pressure (NEP) method, has been introduced to detect expiratory FL during tidal breathing, which does not require either performance of FVC maneuvers on the part of the patient or a body plethysmograph.\(^14\),\(^15\) This method has can also been applied to patients receiving mechanical ventilation.\(^14\) The NEP method has been validated by concomitant determination of isovolume flow-pressure relationships.\(^14\)

**NEP Method for Detection of Expiratory FL**

Figure 2 illustrates the experimental setup used to detect expiratory FL with the NEP method. It consists of a pneumotachograph and a Venturi device capable of generating a negative pressure when connected to a source of compressed air. The Venturi device is activated by opening a rapid solenoid valve. The NEP method consists in applying negative pressure at the mouth during a tidal expiration and comparing the ensuing V˙-V curve with that of the previous control expiration. Therefore, with this technique, the volume and time history, as well as the intrathoracic pressures, during the expiration with NEP are the same as in the preceding control breath. If application of NEP elicits increased flow over the entire range of the control Vt, the patient is not flow limited (Fig 3, left panel). In contrast, if with NEP the subject exhales along part or the entire control V˙-V curve, FL is present (Fig 3, middle and right panels). The FL portion of the tidal expiration can be expressed as percentage fraction of the control Vt (percent Vt). In the two FL subjects in Figure 3, FL amounted to 45% and 68% of Vt, respectively. If expiratory FL is present when NEP is applied, there is a transient increase of flow (spike in Fig 3, right panel), which mainly reflects enhanced dynamic airway compression and sudden reduction in volume of the compliant oral and neck structures.\(^14\),\(^15\) Such spikes are useful markers of FL.

**Relationship of FEV\(_1\) to FL**

Figure 4 depicts the relationship between FEV\(_1\) percent predicted and FL in 117 stable COPD patients. Expiratory FL was determined during resting breathing in sitting and supine positions. Although, on average, the patients who were experiencing FL when both seated and supine had a significantly lower FEV\(_1\) percent predicted than those who were not experiencing FL (p < 0.001), there was marked scatter of the data. Indeed, 60% of the non-FL group had an FEV\(_1\) < 49% predicted, and would
be classified as having severe to very-severe airway obstruction.\textsuperscript{16} Thus, FEV\textsubscript{1} is not a good predictor of tidal expiratory FL.

\section*{FL and Chronic Dyspnea}

Intuitively, one would expect patients with the most severe airway obstruction, as assessed with routine lung function measurements, to be the most dyspneic. However, some patients with severe airway obstruction are minimally symptomatic, whereas others with little objective dysfunction appear to be very dyspneic.\textsuperscript{17} In fact, many studies have shown that the correlation between chronic dyspnea and FEV\textsubscript{1} is weak.\textsuperscript{4} In contrast, FL as measured with the NEP technique is a much better predictor of chronic dyspnea than FEV\textsubscript{1}.\textsuperscript{4,12,13}

\section*{FL and Exercise Capacity}

Since in COPD the reduced exercise capacity shows only a weak relation to FEV\textsubscript{1} and FVC,\textsuperscript{18} it has been concluded that other factors, such as peripheral muscle...
weakness, deconditioning, and impaired gas exchange, play a predominant role to reduced exercise tolerance. A recent study, however, has shown that in COPD there is a strong correlation (r = 0.81) between the resting inspiratory capacity and the exercise capacity. Accordingly, lung function impairment is probably an important cause of decreased exercise tolerance in many COPD patients. Indeed, because of expiratory FL, the maximal V̇ₐ decreased exercise tolerance in many COPD patients. Hence ventilation is closely related to resting inspiratory capacity. FL is a reliable tool for detecting expiratory FL both at rest and during exercise. The method does not require a body plethysmograph, does not depend on patient cooperation and coordination, and can be applied in any desired body posture.

ACKNOWLEDGMENT: We thank Ms. Angie Bentivegna for typing this manuscript.

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Animal Models for COPD*

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(CHEST 2000; 117:223S–227S)

Abbreviations: α₁-AT = α₁-antitrypsin; MMP = matrix metalloproteinase; MMP-12/−/− mice = macrophage elastase-deficient mice; MMP-12+/+ mice = wild-type mice; NE = neutrophil elastase; PPE = porcine pancreatic elastase

Animal models were critical in ushering in the modern era of COPD, after Gross et al. found that intratracheal administration of papain resulted in emphysema in experimental animals. This discovery, combined with the clinical finding by Laurell and Eriksson that patients with α₁-antitrypsin (α₁-AT) deficiency were at increased risk for emphysema, formed the scientific basis for the elastase-antielastase hypothesis for the pathogenesis of emphysema. Today, 35 years later, the elastase-antielastase hypothesis is still the prevailing theory for the development of emphysema, and animal models of COPD remain a critical experimental tool.

ELASTASE-INDUCED EMPHYSEMA

Since initial experiments of Gross et al., investigators have instilled a variety of proteinases into the lungs of many small and large animals. The administration of porcine pancreatic elastase (PPE; 1 to 4 mg/kg) has produced the most consistent and impressive airspace enlargement in rodents, guinea pigs, dogs, and primates. Instillation of PPE results in rapid and significant airspace enlargement, followed by acute neutrophil and subacut...