The Epidemiology, Etiology, Clinical Features, and Natural History of Emphysema

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DEFINITION AND HISTORY OF EMPHYSEMA

The term emphysema derives directly from the Greek word emphysēma, meaning inflation (from the verb emphysisin, to inflate, or blow in). It is defined as abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of their walls and without obvious fibrosis. This destruction results in the loss of acinar structure, and a subsequent reduction in the area available for gas exchange (Fig. 1). The associated loss of elastic tissue leads to small airway collapse and the gas trapping that is often a prominent feature of the disease. Clinically, emphysema is part of the spectrum of disease encompassed by the term “chronic obstructive pulmonary disease” (COPD) that also covers chronic bronchitis, which is a chronic productive cough for 3 months during each of 2 consecutive years (other causes of cough being excluded). The cardinal feature of both emphysema and bronchitis is airflow obstruction.

Frederick Ruysch,1 a professor of botany in Amsterdam and famous for his human anatomic preparations, as well as discovering many anatomic structures (including the bronchial vessels) provided the first recognized description of emphysema in 1691 (Fig. 2). In the 1799 engravings published to illustrate his famous work, The Morbid Anatomy of Some of the Most Important Parts of the Human Body, Matthew Baillie2,3 produced the first detailed illustrations of emphysema. Subsequent work by great minds such as Laennec4 and Orsos5 further characterized the disease, with the realization that disruption of the elastic fibers of the distal airways was the primary underlying pathology.

The recognition of different pathologically patterns of emphysema first came about from the work of Gough and colleagues6,7 in Cardiff in the 1950s, and can now be divided into three subtypes: centrilobular, panacinar, and paraseptal. Centrilobular emphysema is characterized by the loss of respiratory bronchioles with a degree of sparing of the distal alveoli, and predominantly affects the upper portions of the lung. This pattern is the one that is most commonly seen in smokers. Panacinar emphysema affects the entire acinus uniformly; is seen predominantly in the lower lobes; and is the pattern most associated with α-1 antitrypsin deficiency. Paraseptal (also known as distal acinar) emphysema is localized around the septae and pluera, and affects the distal acinar structures. Although often co-existing with centrilobular emphysema in smokers, it can be an incidental finding in young patients and may lead to spontaneous pneumothorax, particularly in apical disease. Bullous emphysema develops from the local expansion of air spaces owing to air trapping, and, in giant bullous disease, can cause significant compression of remaining lung tissue.

However, the distribution on imaging rather than the histologic pattern of disease is probably more useful clinically, because lung volume reduction...
surgery has been shown to benefit those with a predominance of upper lobe disease,8 and endobronchial valve trials have been designed with this same patient group in mind.9,10

DIAGNOSIS

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as “a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.” This definition recognizes the permanent loss of lung function, as well as the often-neglected nonpulmonary components of the disease. The diagnosis of COPD relies on spirometric measurements of forced vital capacity (FVC) and post-bronchodilator forced expiratory volume in 1 second (FEV₁), the most widely used criteria being those defined by GOLD. The diagnosis requires an FEV₁/FVC ratio of <0.7, and patients are then stratified into four categories from mild to very severe disease based on the severity of FEV₁ impairment as set out in Table 1 below.11 The original GOLD publication separated moderate disease into stage IIa and IIb,12 but the staging was later changed such that IIb has become III (severe) and stage IV (very severe) has been added. More recently, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has published its own guidelines, which differ slightly from the GOLD criteria.13 While maintaining the need for an FEV₁/FVC ratio of <0.7, it has done away with the most mild category of disease all together, with an FEV₁ of <80% predicted required to establish the diagnosis.

As the degree of airflow obstruction increases, so too, in general, does the degree of physical limitation and frequency of exacerbations, although there is considerable individual variation in symptom severity.

EPIDEMIOLOGY

COPD is a common and under-diagnosed problem. The World Health Organization (WHO) estimates that 210 million people worldwide suffer from the disease, and that it led to over 3 million deaths globally in 2005 (5% of all deaths).14 It is thought that around half of all COPD cases in the developed world remain undiagnosed, and this proportion is likely to be higher still in the
developing world. Data from NHANES III\textsuperscript{15} indicated that, at the end of the 20th century, 24 million Americans were living with impaired lung function, with 10 million of those reporting physician-diagnosed COPD. Eight million physician consultations, 1.5 million emergency department attendances, and 726,000 hospital admissions were attributed to COPD, with 119,000 deaths. Similar data is available for England and Wales, and the most robust recent data estimates 900,000 people with a diagnosis COPD,\textsuperscript{16} although the true number is likely to be closer to 2 million. Over 100,000 admissions account for over 1 million bed-days, and the disease is thought to cost the National Health Service nearly £1.5 billion annually,\textsuperscript{13} a huge strain on the public purse.

The accumulation of tobacco smoking (or other risk factor exposure) required to cause destructive lung disease means that emphysema is predominantly a disease of middle and late adult life. Disease is often seen earlier in $\alpha$1-antitrypsin deficiency, especially in those who also smoke, but isolated cases of early onset smoking-related disease in the absence of $\alpha$1-antitrypsin deficiency are occasionally seen.\textsuperscript{17}

Historically, COPD has been a male-dominated disease, but the increase in female smokers in the developed world and the increased risk of exposure to biomass fuels in developing countries has led to an equal distribution between the sexes. 90% of all deaths from COPD are thought to occur in the developing world,\textsuperscript{14} where health care systems are absent or insufficient. This situation is mirrored to some extent in developed countries, were there is an association with lower social class. Many factors play a role here, and include smoking status, occupational history (manual labor and exposure to dusts and fumes), and poorer utilization of available health resources.

### Table 1

**Chronic obstructive pulmonary disease staging by FEV\textsubscript{1}**

<table>
<thead>
<tr>
<th>GOLD Staging</th>
<th>NICE Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I: Mild</strong></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC &lt;70%</td>
<td></td>
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<tr>
<td>FEV\textsubscript{1} ≥ 80% predicted</td>
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<tr>
<td>Airflow limitation not meeting criteria for a diagnosis of COPD</td>
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<tr>
<td><strong>Stage II: Moderate</strong></td>
<td></td>
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<tr>
<td>FEV\textsubscript{1}/FVC &lt;70%</td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1} &lt;80% predicted</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC &lt;70%</td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1} &lt;80% predicted</td>
<td></td>
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<tr>
<td><strong>Stage III: Severe</strong></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC &lt;70%</td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1} &lt;50% predicted</td>
<td></td>
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<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC &lt;70%</td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1} &lt;50% predicted</td>
<td></td>
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<tr>
<td><strong>Stage IV: Very severe</strong></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC &lt;70%</td>
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<tr>
<td>FEV\textsubscript{1} &lt;30% predicted or</td>
<td></td>
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<tr>
<td>FEV\textsubscript{1} &lt;50% predicted</td>
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<tr>
<td>with chronic respiratory failure</td>
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<tr>
<td>Severe</td>
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<tr>
<td>FEV\textsubscript{1}/FVC &lt;70%</td>
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<td>FEV\textsubscript{1} &lt;30% predicted</td>
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### ETIOLOGY

Tobacco Smoke

Tobacco smoking is by far the single most important factor in the development of emphysema, and accounts for 80%–90% of cases in the developed world. The decline in FEV\textsubscript{1} with smoking was shown by Fletcher and Peto in 1977,\textsuperscript{18} but they had suggested that only a minority of smokers would go on to develop clinically significant airflow obstruction. This analysis led to the erroneous belief that there were effectively two populations of smokers: those who were resistant and those who were susceptible. Subsequent work over the years has shown that the amount of tobacco smoked is strongly correlated to the degree of emphysema and airflow obstruction, and it is now increasingly apparent that there is a continuum of susceptibility which is likely due to the interplay of a number of genetic and other environmental factors.

The increasing use of cannabis has led to the recognition of emphysematous lung disease, often bullous in nature, in some users. The degree to which lung destruction can be attributed to the cannabis itself is uncertain, however, as studies are confounded by the mixing of the drug with tobacco when smoking, and the use of deeper inhalation and breath holding for maximal effect.

### Genetics

The most well-known genetic association with emphysema is that of $\alpha$-1 antitrypsin deficiency, discovered in 1963 by Carl-Bertil Laurell,\textsuperscript{19} a remarkable biochemist known for his discoveries of transferring,\textsuperscript{20} caeruloplasmin,\textsuperscript{21} and haptoglobin,\textsuperscript{22} and for a crucial role in the description of Waldenström's macroglobulinaemia (named after his collaborator).\textsuperscript{23} In addition to its importance in the field of emphysema, the discovery led to the identification of a new class of
conformational protease inhibitors, the serpins, crucial in many biologic processes including coagulation and inflammation. A detailed discussion of the condition is beyond the scope of this article, but a brief description of the more important aspects follows.

The α1-antitrypsin gene is found on chromosome 14, and α1-antitrypsin is produced in the liver. Mutations of this gene lead to abnormal protein folding with altered secretion from hepatocytes, and subsequent low circulating blood levels. α1-antitrypsin is a wide-ranging antiprotease, but its most relevant activity in respect to the lungs is its action against neutrophil elastase, released from neutrophils at areas of inflammation and in response to tobacco smoke. A lack of α1-antitrypsin allows unopposed elastase activity and subsequent destruction of the lung architecture. While previously thought to be largely a disease affecting those of European descent, it is now recognized that the disease affects a wide range of geographic and ethnic populations.

There are over 75 alleles of the α1-antitrypsin gene (designated Pi). The normal allele is PiM, with PiS and PiZ the two most common abnormal expressions. It appears that only one normal allele is required to produce a normal phenotype, even though these individuals (PiMS, PiMZ) have lower serum α1-antitrypsin levels than PiMM individuals. Apart from very rare null alleles, PIZZ is associated with the most severe clinical picture, as not only are levels severely reduced, but the activity of the gene product is also diminished. The onset of clinical disease is variable, but it is usually evident by the fifth or sixth decade, and roughly 20 years earlier in those who smoke.

Many other genes have been implicated in the pathogenesis of emphysema. Hersh and colleagues have identified single nucleotide polymorphisms associated with different clinical features of advanced emphysema, including dyspnoea (transforming growth factor-beta1 [TGFβ1]), exercise tolerance (latent transforming growth factor-beta binding protein-4 [LTBP4]), and gas transfer impairment (epoxynhydrase 1 [EPHX1]), and gene polymorphisms in glutathione S-transferase p1 (GSTP1), EPHX1, and matrix metalloproteinase 1 (MMP1) have recently been shown to be correlate with upper-lobe predominant disease. This last finding is interesting, as altered function in these xenobiotic enzymes may alter detoxification of cigarette smoke metabolites.

Early-Life Influences

Although emphysema is traditionally thought of as an adult disease, there is mounting evidence that early-life events are important in the development of disease in later life. Prenatal exposure to cigarette smoking is associated with measurable and significant declines in mid-expiratory flow rates (and to a lesser degree FEV1) in childhood, but whether this leads to increased susceptibility to the effects of subsequent smoking is not known. There has also been interest in the role of childhood respiratory infections in the etiology of emphysema. In 1994 the MRC Environmental Epidemiology Unit published compelling data showing the relationship between childhood pneumonia and impaired FEV1 in adulthood, although recently published data from the British 1958 Birth Cohort, suggest that the rate of decline in lung function in midadulthood life is unaffected.

Bronchopulmonary dysplasia, a disease of prematurity in neonates treated with oxygen and mechanical ventilation, leads to airflow obstruction, hyperinflation, and areas of emphysema on CT in those who survive to adulthood. Although rare, it is likely to become an increasingly frequent cause of obstructive lung disease in the adult respiratory clinic.

Industry

It has become clear that a higher prevalence of emphysema is seen in workers in several occupations associated with exposure to fumes, chemicals, and dusts. The most extensively researched of these is the coal industry, with reports as far back as the late 1940s. Exposure to respirable dust particles (<0.1<sub>μ</sub>m) and α-quartz (P < .02) in Norwegian tunnel workers was shown to result in an excess decline in FEV1 of 25-38ml/yr in non-smoking workers, and studies in gold miners have demonstrated higher rates of emphysema at post-mortem in those with long term exposure to underground mineral dust. Many such examples exist in the literature, and it is likely that any occupation in which workers are chronically exposed to a mixture of noxious fumes and airborne particles will confer an additional risk of emphysema on those workers, and this effect seems particularly prominent in those who also smoke. Knowledge of such associations is important when giving advice about continued employment, and often compensation issues arise.

Biomass Fuels

Indoor exposure to smoke from biomass fuels (wood, crop residues, charcoal, and dung) used for cooking and heating is now recognized as a major cause of COPD worldwide, and causes widespread emphysema on CT imaging. It kills 1.6 million people every year of whom one million
are children, and the WHO estimates that it is responsible for 22% of all cases of COPD. The problem is disproportionately prevalent in women in the developing world, who can spend many hours a day around the cooking fire. A survey of over 20,000 citizens in southern China found an excess of COPD in those with poor ventilation in the kitchen and previous exposure to biomass fuels, with a degree of risk similar to a 15–30 pack year smoking history.

British versus Dutch Hypothesis

The Dutch hypothesis, as it became known, postulated that asthma and COPD existed as part of a spectrum of lung disease ("chronic nonspecific lung disease") that resulted from any number of airway irritants leading to inflammation and declines in lung function. This theory seems appealing when one considers those patients with COPD with a degree of reversibility, or those with progressive asthma symptoms; however, inflammatory mediators in the two conditions are very different. An alternative theory, the British hypothesis, suggested that chronic airflow obstruction in smokers was a result of recurrent airway infections, with those getting more frequent infective episodes having the more rapid decline in lung function. This theory was discounted some 17 years later after a study by Fletcher and colleagues, but it has recently been revived with reports of more rapid lung function decline in those with recurrent respiratory tract infection and higher sputum bacterial counts.

PATHOPHYSIOLOGY AND CLINICAL FEATURES

The inhalation of noxious particles and fumes leads to a disruption of the mucociliary escalator, inflammation, and tissue damage resulting in airflow obstruction and a variable degree of chronic sputum production. Lung defenses are altered, and there is a greater susceptibility to bacterial infection and colonization, exacerbations and perpetuation of the inflammatory process, and impaired quality of life.

On pulmonary function testing, there are reductions in all dynamic lung volumes, and graphical representations of flow and volume are characteristic. There is a scalloping of the expiratory flow-volume loop, with an increasingly severe and early pressure-dependent small airway collapse and flow reduction as the disease progresses. In contrast, static lung volumes show hyperinflation with increases in total lung capacity (TLC) and residual volume (RV), and gas trapping is manifested as an elevated RV/TLC ratio. These features lead to the typical chest radiograph of large lung volumes, hyperlucent lung fields, and flattened diaphragms (Fig. 3). The elastic recoil forces of the lung and the outward elastic forces of the chest wall are in equilibrium at functional residual capacity (FRC). With the slowly progressive destruction of lung tissue that underlies emphysema, the recoil forces of the lung become diminished, and FRC is shifted along the lungs compliance curve of the lungs to the detriment of pulmonary mechanics. This situation is exacerbated during exercise when ventilatory requirements are increased. Airflow obstruction and prolonged expiratory time mean that expiration cannot be completed before the urge to inspire, with inhalation triggered before FRC is reached. This dynamic leads to "stacking" of breaths and a gradual hyperinflation of the lungs, known as dynamic hyperinflation. Work of breathing is subsequently increased via two mechanisms. Firstly, the rightwards shift along the compliance curve requires a larger change in pressure (and hence effort) to generate a comparable tidal volume (VT). Secondly, the creation of an artificially high end-expiratory lung volume, or dynamic FRC, means that residual elastic recoil forces must be overcome before negative intrathoracic pressures are generated and inspiratory airflow can begin: intrinsic PEEP (PEEPi). These mechanisms are illustrated in Fig. 4.

The loss of distal airway structures reduces the effective surface area of the lung and hence the area available for gas exchange, and the associated disruption of the alveolar-capillary architecture over

![Fig. 3. Typical chest radiograph of a patient with emphysema demonstrating the hyperexpansion, hypertransradiance, and flattened diaphragms caused by air trapping.](image-url)
time leads to ventilation-perfusion (V/Q) mismatch. As arterial carbon dioxide (CO₂) levels are inversely correlated with alveolar ventilation, CO₂ levels can initially be maintained in the face of hypoxia by an increase in the minute volume. As the disease advances, there is an increase in physiologic dead-space secondary to under-perfused alveoli, and the subsequent impairment of CO₂ clearance results in hypercapnic respiratory failure.

Pulmonary arterial hypertension (PAH) may develop in any severe lung disease, and thus is seen in patients with advanced emphysema, exacerbating breathlessness and worsening exercise tolerance. There appears to be a subgroup of patients in whom there is a disproportionate degree of PAH,⁴⁴ the mechanisms for which are not clear but may be genetic in origin.⁴⁵ Although there has been burgeoning interest in the use of pulmonary vasodilators in patients with secondary PAH, robust evidence for their use is lacking. Nonetheless, a referral to an expert in the field should be considered for those with significant or symptomatic PAH for enrollment in clinical trials.

Increasing recognition has been given to the nonpulmonary aspects of obstructive airways disease over recent years. Arguably the most important of these is peripheral muscle weakness, particularly of the quadriceps muscles, the strength of which has been shown to predict mortality in moderate to severe COPD.⁴⁶ The etiology appears to be multifactorial, including disuse atrophy, the effects of systemic steroid therapy, and genetic factors. Work by Hopkinson and colleagues⁴⁷ has shown associations between quadriceps strength and genotypes of the angiotensin converting enzyme (ACE) and vitamin D receptors,⁴⁸ potentially exciting targets for future therapies.

Collateral ventilation is the ventilation of alveolar structures through passages or channels that bypass the normal airways, and occurs through interalveolar (pores of Kohn, who originally thought them pathological⁴⁹), bronchioalveolar (channels of Lambert), and interbronchiolar (channels of Martin) connections. These high-resistance channels are clinically unimportant in health, but as airflow obstruction increases in the emphysematous lung, airways resistance approaches collateral resistance and collateral airflow increases.⁵⁰ This recruitment of collateral channels is assisted by hyperinflation, because there is an inverse relationship between resistance in collateral channels and lung volume.⁵¹ With the advent of endobronchial valve treatments for upper-lobe predominant heterogeneous emphysema, there is a renewed interest in measurements of collateral ventilation. Results from the endobronchial Valves for Emphysema palliatioN Trial (VENT; Sciurba F, unpublished data, 2007) showed that those with incomplete fissures on lung CT did not derive the same degree of benefit from valve placement as those with complete fissures, the inference being that collateral channels continued to aerate the treated segments preventing volume loss.

**NATURAL HISTORY**

COPD is recognized as a progressive disease, both in terms of symptoms and clinical measures of disease activity. Those with GOLD stage I disease usually have no symptoms or signs, in keeping with the very mild degree of airflow limitation. Symptoms then largely progress as outlined below, although there is considerable individual variation.

**Stage II**

No abnormal signs, have little or no breathlessness, and symptoms are limited to a “smoker’s cough.”

**Stage III**

Onset of breathlessness with or without wheeze on moderate exertion, a productive cough, and abnormal signs such as a general reduction in breath sounds and the presence of wheeze.

**Stage IV**

Breathlessness on any exertion and even at rest, with prominent wheeze and cough, hyperinflation, and the eventual development of cyanosis, peripheral edema and polycythaemia, especially during exacerbations.
Never-smokers show a loss of FEV1 at approximately 40 mls per year but almost never reach a level at which they are disabled by reduced airflow. Even in light smokers, there is an additional accelerated decline, and a similar relationship almost certainly exists with exposure to any number of noxious stimuli, but a return to the usual age-related decline is seen on their withdrawal.18 There may also be an accelerated loss with advancing age.52 As lung function is already impaired on removal of any exposure, the subsequent natural fall results in development of worsening disability, as illustrated in Fig. 5.

As emphysema comes under the umbrella of COPD, there is limited information on the natural history of emphysema per se. The National Emphysema Treatment Trial (NETT)8 resulted in the collection of a large amount of follow-up data on this specific population of patients, with information regarding progression of lung function, symptoms, health status, exercise capacity, and mortality. The May 2008 issue of the Proceedings of the American Thoracic Society published a series of articles analyzing this data, and the findings are summarized below.

COPD patients are known to have an impaired quality of life, which worsens with deterioration of lung function53 and time,54 findings that were replicated in the NETT.55 Those patients treated medically also had a progressive decline in exercise capacity as measured by cycle ergometry. Mortality was correlated with a number of clinical and physiologic measures. Higher RV and lower TLC were independently predictive of mortality in multivariate analysis, but the value of the FEV1 was only significant on univariate analysis. Those patients with more homogenous or lower-lobe predominant emphysema fared worse; and lower exercise tolerance and age were also significant predictors. Of 609 patients in the medically treated cohort, 292 had died as of September 2005, after a median follow-up of only 3.9 years (12.7 deaths per 100 person-years).56

In keeping with a more multisystem approach to COPD, multifactorial scoring systems have been developed to provide a better indication to prognosis. The most established of these is the BODE score, incorporating BMI, the degree of airflow Obstruction, Dyspnoea, and Exercise capacity.57 The total score obtained correlates better than the FEV1 with all-cause and respiratory mortality, and analysis of the NETT data shows that the change in a modified BODE score is of further short and intermediate term prognostic value.58

Acute Exacerbations

Acute exacerbations of COPD, as well as the obvious short-term impacts, have more far reaching consequences. There is subsequently a more rapid decline in FEV1,42 and exacerbations requiring hospital admission have a significant risk of mortality attached to them, with around 10% dying in hospital, and a 23%–43% 1-year mortality rate.59,60 Mortality figures are even worse when the presentation is one of acute hypercapnic respiratory failure, with over half of those requiring invasive ventilation not surviving to discharge.61 In those who survive their admission, 80% will be readmitted and approximately 50% will be dead at one year.62 The increase in noninvasive ventilation facilities has improved immediate survival, and early pulmonary rehabilitation improves exercise capacity and health status at 3 months,63 but exacerbations still represent one of the most dangerous aspects of the disease.

SUMMARY

The burden of disease attributable to emphysema is significant and growing, and is a leading cause of disability in middle and late life. There has
traditionally been a rather nihilistic attitude toward emphysema and COPD, but with recent advances in the understanding of aetiological, pathophysiological, and prognostic mechanisms, and the increase in treatment options, this approach is no longer appropriate.

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