Staging of COPD

COPD in the ECRHS

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More work is needed on the concept of staging of COPD

As a junior doctor I once worked in a hospital where the leading consultant in medicine refused to accept the diagnosis of asthma in patients older than 40 years. To him, airflow obstruction was ''asthma'' in the young and ''chronic bronchitis'' in the elderly. While it soon became apparent that asthma *does* occur after the age of 40, the likelihood of significant airflow limitation occurring in young adults who have never had asthma has always seemed small to me. In this issue of *Thorax* De Marco *et al* describe the prevalence of chronic obstructive pulmonary disease (COPD) in young adults taking part in the European Community Respiratory Health Survey (ECRHS).[1] They found COPD to be a considerable issue; in total, 3.6% had COPD stage I+ according to the NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD)[2] and 11.8% had chronic respiratory symptoms without airflow limitation—that is, COPD GOLD stage 0.

The study raises several questions relating to methodology, findings, and interpretation. Diagnosis and staging of COPD was done according to the GOLD guidelines[2] using an FEV_1/FVC ratio of 0.7 and FEV_1 cut off points of 80%, 50%, and 30%. In subjects aged 20–44 years a ratio of 0.7 will not overestimate airflow obstruction—more likely it will underestimate it. The major challenge seems to be exclusion of asthma and the approach of De Marco *et al* can, to some extent, be questioned. In contrast to GOLD recommendations, prebronchodilator FEV_1 was used for staging but this seems acceptable in the epidemiological setting where administration of bronchodilators is often not feasible. Patients with self-reported asthma without cough/phlegm were excluded while those with both self-reported asthma and chronic symptoms were considered to have COPD with coexisting asthma. The latter seems intuitively correct in a 44 year old heavy smoker with a smoking history of 30 pack years, but is it true in the 20 year old never smoker with self-reported asthma? Unfortunately, no valid answers exist; GOLD has not attempted to separate stage 0 COPD from symptomatic asthma, and only for subjects with irreversible airflow limitation does GOLD acknowledge the problem: ''Poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis, tuberculosis, or asthma is not included except insofar as these conditions overlap with COPD''.[2] In the Copenhagen City Heart Study cohort[3] 54% of women and 63% of men with self-reported asthma had chronic productive cough; this will presumably remain an issue for debate for some time.

COPD stage 0 denoting subjects ''at risk'' was introduced by GOLD, but the concept cannot be regarded as evidence based and remains controversial.[4 5] It is, nevertheless, intriguing that the prevalence of chronic symptoms in 20–44 year old subjects is more than 10% on average and as high as 24% in Spain. Risk factors did not differ substantially between stages 0 and I+, and a recent Italian study has shown that stages 0 and I differ little in health status.[6] Still, we do need prospective studies of stage 0 including various outcomes. We also have to make clear the reason for applying staging to COPD. Undoubtedly, staging facilitates communication and comparison of study results. It is, however, less clear that it reflects biological changes over time. The concept of cancer staging—where, by definition, patients progress through the stages—may not be valid in COPD. While it is unlikely for anyone to have stage III or IV without passing through earlier stages, COPD stage I can undoubtedly develop without the patient ever having been in stage 0.[4] Years of looking at the ''Fletcher diagram''[7] have anchored the impression of rapid decline so firmly in our minds that we may tend to forget that, through impaired growth of lung function in childhood and early adolescence, any superimposed airflow obstruction at a later age could very well start the patient off in COPD stage II.[8] For this and other reasons, more work on the concept of staging of COPD is clearly needed.

COPD is a burden in the elderly, but it is not a disease of the elderly alone. The notion of COPD in young adults was confirmed by the ''confronting COPD'' study,[9] but whereas that study used doctor's diagnosis and presence of symptoms, the ECRHS study has verified the diagnosis with spirometric testing in random population samples, enabling us to quantify the problem. Unfortunately, the study by De Marco *et al* does not tell us the prevalence of doctor diagnosed COPD in their cohort. COPD is often undiagnosed[10] and, based on data from the IBERPOC study, this is even more so in younger patients[11] and in women more than in men.[11 12] In this respect, the ECRHS study showed COPD to be more prevalent in men than in women. When biological explanations are applied to these findings, caution is probably warranted. Better information is available in this area from longitudinal studies[13] and, in addition, detailed information on smoking such as age of starting and inhalation is essential for adjusting properly for sex differences in smoking habits when addressing susceptibility.[14]

With the study by De Marco *et al*, however, COPD epidemiologists now have to join asthma epidemiologists in praising the ECRHS. One important question remains: How should these findings change our perception of COPD? They probably should not! The strengths of the paper lie in the finding that COPD is a widespread problem in young adults and the implications of the quantification. To limit case finding and/or screening for COPD to middle aged or elderly subjects would be missing a window of opportunity based on these findings.

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Oxygen sensing

New insights into oxygen sensing at a cellular level

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The oxygen sensing pathway offers a new set of therapeutic targets for conditions ranging from inflammatory lung disease to pulmonary hypertension

The ability of cells to detect and respond to a fall in oxygen tension is of fundamental importance for maintaining oxidative metabolism and tissue homeostasis. One of the challenges facing scientists working in this area has been that any proposed mechanism for oxygen sensing has to accommodate the very different tolerances of certain tissues to hypoxia and the extreme variation in the cellular responses observed. Hence, while skeletal muscle cells can recover function after 30 minutes of anoxia, the brain suffers irreparable damage after only 4–6 minutes of ischaemia.[1] Moreover, while carotid body cells respond to changes in oxygen tension that barely register in non-chemosensory tissues (and do so within seconds),[2] upregulation of erythropoietin synthesis in the interstitial peritubular cells is transcriptionally regulated and requires far more protracted periods of hypoxaemia.[3] Despite such variances in oxygen sensitivity and response time, all cells appear capable of responding to hypoxia and the essential components of a universal oxygen sensing mechanism have at last begun to emerge. Moreover, from studies conducted in stroke and heart disease, it is apparent that therapeutic targeting of this novel pathway is set to transform our approach to pathology previously deemed intractable.

RESEARCH STUDIES

Initial clues into how cells respond to low oxygen came from studies undertaken in the early 1990s examining the hypoxic response element (HRE) of the erythropoietin (Epo) gene. This led to the identification of a transcriptional activator called hypoxia inducible factor (HIF).[4] HIF is a heterodimer composed of HIF-1β (or aryl hydrocarbon receptor nuclear translocator, ARNT), which is constitutively expressed, and HIF-1α whose expression and transcriptional activity are tightly regulated by the ambient oxygen concentration.[5] Once formed, this protein complex migrates to the cell nucleus and, together with the co-activator CBP/p300, binds to the HREs present on the promoter region of genes involved in regulating metabolic supply and demand.[6] Examples of HIF regulated genes include those involved in regulating vascular tone (for example, iNOS and adrenomedullin), angiogenesis (for example, vascular endothelial growth factor, VEGF), cell metabolism (for example, lactate dehydrogenase A, the glucose transporter GLUT-1), and haemoglobin biosynthesis (for example, erythropoietin).[7] These findings, together with the ubiquitous nature of HIF and the demonstration that HIF deficient animals show major defects in many core physiological responses to oxygen, have resulted in HIF being regarded as one of the master regulators of the cellular response to hypoxia.[8]

The next step in this quest was to define the mechanism responsible for hypoxic induction of HIF-1α. Through a combined structural and genetic approach, it has now been possible to show that HIF-1α activity is regulated by enzymatic hydroxylation at specific prolyl and asparaginyl residues by a novel 2-oxoglutarate dependent class of dioxygenases.[9] Critically, these enzymes have been shown to display an absolute requirement for oxygen in addition to iron (Fe^{2+}) and ascorbate. These oxygen sensitive enzymes inhibit HIF activity in a complementary manner since the prolyl hydroxylase domain containing enzymes (PHDs) result in an interaction between HIF-1α and the von Hippel-Lindau protein which targets HIF-1α for proteosomal destruction,[10] and factor inhibiting HIF (FIH) causes asparaginyl hydroxylation and blocks HIF association with CBP/p300.[11 12] Hence, under normoxic conditions, HIF-1α levels remain low and this prevents the transcription of genes containing HRE promoters (fig 1).

CLINICAL APPLICATIONS

How does this inform our understanding of the pathophysiology of lung disease and can it provide the basis of novel therapies? Mice homozygous for a null mutation in the HIF-1α[13] or HIF-1β genes[14] die at mid gestation with vascular defects primarily involving the embryonic and extraembryonic circulation, respectively. In contrast, HIF-$1\alpha^{+/-}$ mice develop normally and are indistinguishable from wild type littermates. However, when exposed to 10% oxygen for up to 6 weeks, the HIF-$1\alpha^{+/-}$ mice demonstrate reduced susceptibility to pulmonary hypertension, polycythemia, and right ventricular hypertrophy relative to their wild type littermates.[15] Morphometric analysis showed that the chronically hypoxic HIF-$1\alpha^{+/-}$ mice have fewer completely muscularised pulmonary arterioles and the degree of muscularisation in such vessels is reduced compared with HIF-1α wild type mice. Thus, HIF-1 appears to play a major role in mediating pulmonary vascular remodelling in chronic hypoxia, and therapeutic manoeuvres that inhibit HIF-1 activity in the lung may slow the progression

Abbreviations: ARNT, aryl hydrocarbon receptor nuclear translocator; FIH, factor inhibiting HIF; HIF, hypoxia inducible factor; HRE, hypoxic response element; PHD, prolyl hydroxylase domain containing enzyme