AIRWAY HYPERRESPONSIVENESS AND COPD MORTALITY

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Introductory article

Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study

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*Background: Smoking and airway lability, which is expressed by histamine airway hyperresponsiveness, are known risk factors for development of respiratory symptoms. Smoking is also associated with increased mortality risks. We studied whether airway hyperresponsiveness is associated with increased mortality, and whether this risk was independent of smoking and reduced lung function. Methods: We followed up 2008 inhabitants of the communities of Vlagtwedde, Vlaardingen, and Meppel (Netherlands), who had histamine challenge test data from 1964–72 for 30 years. Follow-up was 99% successful (29 patients lost to follow-up) with 1453 participants alive and 526 deaths (246 died from cardiovascular disease, 54 from lung cancer, and 21 from chronic obstructive pulmonary disease (COPD)). Findings: Mortality from COPD increased with more severe hyper-responsiveness; relative risks of 3.83 (95% CI 0.97–15.1), 4.40 (1.16–16.7), 4.78 1.27–18.0), 6.69 (1.71–26.1), and 15.8 (3.72–67.1) were associated with histamine thresholds of 32 g/l, 16 g/l, 8 g/l, 4 g/l, and 1 g/l, respectively, compared with no hyperresponsiveness. These risks were adjusted for sex, age, smoking, lung function, body mass index, positive skin tests, eosinophilia, asthma, and city of residence. Interpretation: Increased histamine airway hyper-responsiveness predicts mortality from COPD. Although this trend was more pronounced in smokers, an increasing proportion of COPD deaths with increasing hyper-responsiveness was also present among individuals who had never smoked. (**Lancet** 2000;356:1313–7)*

Airway hyperresponsiveness (AHR) is a feature of airways diseases which has attracted considerable attention. In asthma AHR has become one of the defining features whereas its role in chronic obstructive pulmonary disease (COPD) has caused more debate than clarity. The reason for the debate has mainly been the fact that AHR can be viewed differently, depending on the views and beliefs of the commentator. Measurement of AHR can be seen as just another physiological measurement characterising airway diameter and properties of the airway wall in line with spirometric and reversibility testing. On the other hand, AHR can also be seen to reflect specific characteristics of the airway epithelium, inflammatory cells, and autonomic nervous system, involving a number of mediators of which many have yet to be characterised. Several of these components may be genetically determined and the large number of individual components ensures a large variation. No matter how AHR is viewed, it has attracted interest as a prognostic marker in COPD and, again, in this role it can be viewed as just another prognostic marker in a chronic disease with well characterised slow progression or as one of the key parameters determining the natural history of COPD. It is the latter position which was brought forward in the "Dutch hypothesis".[1] As described previously, the early debate on the Dutch hypothesis unfortunately focused on the pooling of all obstructive airways disease instead of the more interesting possible determinants of susceptibility to tobacco smoking.[2]

AHR AND COPD MORTALITY

Few studies are able to address possible associations between AHR and COPD mortality because of the need for a large sample size and sufficient follow up time. The well known Dutch study from Vlagtwedde, Vlardingen and Meppel examined approximately 2000 subjects with histamine challenge and has followed them for more than 20 years. In the recent mortality study by Hospers *et al*[3] (the introductory article) 526 deaths were analysed; 21 were found to be caused by COPD while in 39 cases COPD was a contributing factor. The authors' interpretation of their analysis is quite clear, stating that increased AHR to histamine predicts mortality from COPD. There are, however, shortcomings that need to be addressed.

There is an undisputed association between airway diameter and AHR which necessitates proper control for lung function in survival studies as lung function is normally a confounder, being associated with exposure, AHR,[4 5] and outcome—that is, death from COPD.[6–8] In the study

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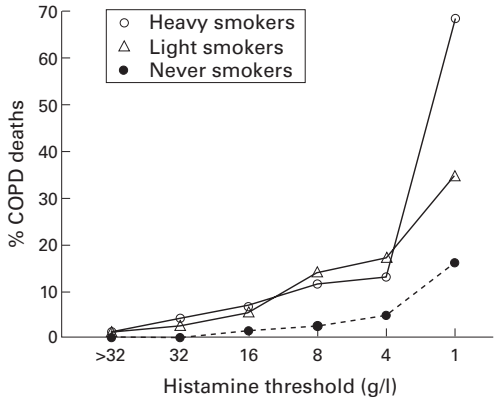

Figure 1 Percentage of deaths with COPD as primary or secondary diagnosis according to the histamine threshold in light, heavy, and never smokers. Modified from Hospers et al[3] with permission.

by Hospers *et al*[3] lung function is included in the analysis as percentage predicted forced expiratory volume in one second (FEV_1) is categorised as >100%, 80–100%, and <80%. These categories are not sufficient to control for lung function. The <80% category seems very wide, and AHR is bound to vary significantly within this group because of the vast differences in airways calibre. The argument by the authors that the stratification of FEV_1 into these three categories reduced the risk associated with AHR only indicates that some—but not necessarily sufficient—control was obtained. This point may seem trivial, but the most important scientific exercise when addressing a new predictor of mortality should be to determine if the association between the new predictor and mortality can be reduced to an insignificant level by already established predictors.

Another issue is the relationship between smoking and AHR in the natural history of COPD. The authors avoid reference to the Dutch hypothesis and thus avoid using AHR as a marker of susceptibility to tobacco smoke. Instead, they position AHR as a measure in its own right. There is, nevertheless, an interaction between smoking and AHR, as the risk of dying from COPD increases in both light and heavy smokers with increasing AHR, as shown in the introductory article[3] and summarised in fig 1. An interaction between smoking and AHR has so far only been shown in the Lung Health Study[9] and, to our knowledge, this is the first time a strong interaction between smoking and AHR has been demonstrated. It should therefore probably have been given greater emphasis. However, a few deaths were registered among never smokers, all of which occurred in subjects with at least some reactivity and in three of five subjects with a histamine threshold of 4 g/l or less. Most clinicians will ask why these hyperresponsive never smokers who died of COPD are not simply patients with asthma? This possibility is not mentioned in the paper although a proportion of asthmatic subjects develop irreversible airflow limitation[10–12] and have a higher risk of dying with a diagnosis of COPD on the death certificate.[13] This probably reflects the inadequacy of correct asthma diagnosis in previous times. We feel confident that such patients would today be given a treatment trial of, for example, four weeks of inhaled corticosteroids which would reveal asthma.

Predictors of overall mortality

In the study by Hospers *et al*[3] AHR was also, to some extent, a predictor of overall mortality and, from the numbers in their paper, it does not seem to be entirely due to the limited number of deaths from COPD. The association with overall mortality has also been observed for other parameters with a clear relation to pulmonary disease, most notably lung function. The association between lung function and survival basically reflects the background to the introduction of spirometric testing by Hutchison in 1846.[14] Both forced vital capacity (FVC) and FEV_1 have a strong predictive value on overall mortality and this prompted Cohen to suggest in 1978 that lung function was the common feature denoting susceptibility to smoking, not just on the lungs and the airways but on the whole organism.[15] The association is, however, also seen with other features of pulmonary disease—for example, chronic hypersecretion of mucus was shown to be associated with overall mortality in one study[16] but not in others.[17 18]

In the Vlagtwedde-Vlaardingen study both eosinophilia and a positive skin prick test were found to be associated with overall mortality, although the association with the skin prick test was only found in those with decreased lung function.[19] An important reason for this was the association between the two indices and cardiovascular mortality, where an interaction with reduced lung function was found.[20]

This raises the question whether an effect on overall mortality is merely due to a "spill over" of predictive value from specific causes of death or whether the significant predictors can be viewed as markers of susceptibility. In geriatric medicine the term "frailty" is often used,[21 22] and it may be worthwhile to ask if all these parameters associated with overall mortality are markers of universal frailty. Statistical methods cannot provide much help in this respect. Estimates of the effects on overall mortality in long term epidemiological studies with a large number of outcomes may be good, but our measures of the association with cause-specific mortality are often determined with such uncertainty that the precise associations can be difficult, if not impossible, to determine. Instead, we must rely on more basic science to disentangle the mechanisms responsible for such broad terms as "susceptibility" or "universal frailty" and then determine the role of non-specific measures from respiratory medicine.

Bronchodilator reversibility as a marker of AHR

As AHR is a feature of obstructive airways disease, so is the responsiveness to a bronchodilator. In general, the responses to a bronchoconstrictor and to a bronchodilator have been considered to reflect the same underlying physiological abnormality, and it has been assumed that the two measures are highly correlated. Thus, provocation challenges have often been replaced with bronchodilator tests, especially in severe airways obstruction where provocation tests are contraindicated. Reversibility testing has also been preferred to provocation challenge because of its simplicity and lack of discomfort to the patient.

The interchangeability of the two measures has, however, been disputed, based on studies demonstrating that the response to a bronchodilator and to a bronchoconstrictor is not always highly correlated, and on studies which have shown that the two measures do not contribute identically in predicting the outcome in obstructive airways disease.

It is evident that correlations will depend on the population under study. Benson[23] found a good correlation (r = 0.83) between the response to histamine and the response to isoprenaline in 19 patients with airways obstruction of mixed aetiology. Likewise, in a study of 57 subjects with chronic bronchitis and no asthma, Campbell *et al*[24] found the

Learning points

- Airway hyperresponsiveness is a predictor of mortality in COPD.
- It is unclear which pathological features are reflected by airway hyperresponsiveness in COPD.
- As in asthma, the response to bronchoconstrictors and bronchodilators reflects different characteristics of the airways in COPD.
- The response to bronchodilators has little if any prognostic value in COPD.

response to a bronchodilator and to methacholine to be significantly related and the two responses were interchangeable as predictors in the multivariate analyses of the decline in ventilatory function.[24] However, in a population based study Douma *et al*[25] found no correlation between the response to histamine and the response to terbutaline in 101 subjects of whom 39 had airways obstruction. Furthermore, only the bronchoconstrictor response was associated with the prevalence of respiratory symptoms while the bronchodilator response was not. The interpretation of these results is complicated by the well known fact that both the bronchoconstrictor and the bronchodilator responses are associated with the initial FEV_1. Thus, in this study there was a weak but significant correlation between the response to histamine and the response to terbutaline if reversibility was measured relative to baseline FEV_1, but this correlation disappeared if reversibility was measured relative to the predicted FEV_1.

Studies of reversibility as a predictor of the decline in FEV_1 have also yielded conflicting results. Two small studies of subjects with COPD found that a high degree of reversibility was associated with a more rapid decline in FEV_1, even after controlling for baseline FEV_1.[24 26] Similar results were found in a population based study by Vollmer *et al* in which subjects who were responsive to isoproterenol, but without manifest clinical disease, were found to have a greater decline in FEV_1 than non-responsive subjects.[27] In contrast to these findings, a large study of 985 patients with COPD by Anthonisen *et al*[28] and a study of 81 patients by Postma *et al*[29] showed that a high degree of reversibility predicted a more favourable outcome in terms of the decline in lung function.

There are several possible reasons for the discrepancy between these studies. Firstly, as recognised by all those who work in the field of respiratory epidemiology, there are considerable methodological problems in analysing longitudinal changes in FEV_1. These problems have been fully discussed in many papers and we will only emphasise that an association between the annual change in FEV_1 and the bronchodilator response might be merely an autocorrelation as postbronchodilator FEV_1 is contained in both parameters. This was also recognised by Anthonisen *et al*[28] who attempted to avoid this problem by not using baseline data in calculating the annual change in FEV_1. Secondly, it has been suggested that regular treatment with bronchodilators is a prerequisite for a beneficial effect on reversibility as such treatment was used in these positive studies.[28 29] However, the Lung Health Study found that regular treatment with a bronchodilator had no effect on the decline in FEV_1.[30] Finally, a beneficial effect of reversibility may be in line with the observations of Burrows *et al*[31] who showed that patients with an "asthmatic type" of COPD had a smaller decline in FEV_1 and a better survival than patients with an emphysematous type of COPD. Thus, reversibility could be a marker associated with a more benign course of COPD. This hypothesis, however, has not gained support from most other survival studies.

The studies on reversibility in relation to survival have provided more uniform results than studies on the decline in FEV_1. The study by Anthonisen *et al*[28] showed that reversibility to a bronchodilator was a positive prognostic factor in relation to survival as long as adjustment was made only for prebronchodilator FEV_1. However, if postbronchodilator FEV_1 was used, the reversibility became non-predictive. Similar results were found in a study by Hansen *et al*[32] of reversibility to corticosteroids in 1095 patients with COPD and 491 with asthma where both bronchodilator and corticosteroid reversibility were found to be unimportant for survival if maximal FEV_1 was controlled for. Postma *et al*[33] argued that survival prediction improved if reversibility was expressed relative to the difference between predicted and baseline FEV_1, in which case reversibility was still significant after controlling for postbronchodilator FEV_1. However, this has not been confirmed in other studies.

Thus, the importance of reversibility as a risk factor in populations and groups of patients with airflow obstruction is far from clear. It is reasonable to assume that pronounced reversibility in an epidemiological context is a marker of AHR and a subsequent rapid decline in FEV_1, as demonstrated by Vollmer *et al*.[27] In patients with established COPD it is not clear whether reversibility has a negative influence on the decline in FEV_1 (acting as a proxy for AHR) or a positive influence (acting as a marker of more benign and treatable disease). The methodological problems are immense, and the most convincing results come from the large study by Anthonisen *et al*[28] which favoured a positive influence of reversibility. However, in relation to survival in COPD, there seems to be no general effect of reversibility per se, and it seems reasonable to conclude that reversibility does not have an important role if smoking and maximal lung function are accounted for. AHR and reversibility are therefore not interchangeable as prognostic markers as AHR has consistently been shown to be a marker of poor prognosis, independent of whether the outcome is FEV_1 or decline in FEV_1[2] or mortality.[3]

AHR in COPD

What, then, does the presence of AHR in COPD indicate? The answer at present is that we simply do not know. Although we may have increasing evidence from respiratory epidemiology for the role of AHR as a risk factor for COPD, we still do not have a full explanation for this. To date, only a few small studies have been performed in the field of AHR and inflammatory markers in COPD. No overwhelming associations have appeared and, furthermore, the interpretation of the results is hampered by the eternal problem of distinguishing asthma from COPD. However, one

thing seems clear and perhaps is so evident that it is often forgotten—the biology underlying AHR is different in asthma and COPD, as indicated by the fact that AHR in asthma responds to treatment with corticosteroids which is not the case in COPD,[34] or only to a modest degree.[35] Thus, the epidemiological research of hyperresponsiveness in COPD is bound up with immense problems as there are at least two diseases, asthma and COPD, which differ in many aspects but can still be very difficult to distinguish in an epidemiological context. Furthermore, patients with these two diseases both have some kind of AHR which is also indistinguishable in an epidemiological setting but can have quite different implications.

As clinicians with a research interest in clinical epidemiology, we look with great interest to our research colleagues in basic science to provide us with some good explanations.

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