Linking ventilation heterogeneity and airway hyperresponsiveness in asthma

Jose Venegas

Heterogeneity indices derived from the multiple breath nitrogen washout technique are strongly associated with AHR in asthma

Airway hyperresponsiveness (AHR), inflammation and heterogeneity in airway constriction and ventilation within the airway tree are fundamental features of asthma. Heterogeneity in ventilation is relevant not only because it affects gas exchange efficiency (ventilation/perfusion in asthma), but also because it can theoretically magnify the degree of mechanical obstruction which could affect the degree of AHR. By thickening of airway walls, increasing airway secretions and releasing mediators, inflammation could also be linked to ventilation heterogeneity and AHR in asthma. Indeed, the exhaled nitric oxide concentration (FENO) is substantially increased by inflammation in asthma and has been proposed as a non-invasive biological marker to guide treatment.

In this issue of Thorax, Downie and coworkers present convincing evidence that ventilation heterogeneity is strongly associated with AHR in patients with asthma, regardless of the level of inflammation (see page 684). In a group of subjects with a wide range of asthma severity, the authors measured, among other parameters, the heterogeneity of the conducting airways by multiple breath nitrogen washout (Scond) and FE\textsubscript{NO} with AHR to methacholine. A subgroup of patients with poorly controlled symptoms was also studied after 3 months of treatment with inhaled corticosteroids. Analysis of the whole group of patients at baseline showed a positive correlation of AHR with FENO and Scond. In a group of patients at baseline showed a positive correlation of AHR with FENO and Scond. In a group of patients at baseline showed a positive correlation of AHR with FENO and Scond. In the subgroup selected for having significantly during bronchoprovocation, the bronchodilating effect of dynamic airway stretching during breathing and the dynamic interactions between airways of the bronchial tree could lead to an inherently unstable system during bronchoconstriction that could magnify any small existing heterogeneity.

The basic mechanism can be visualised by considering two identical daughter branches at an airway bifurcation. Both airways receive equal flows, pressures and tidal volumes, and their behaviour is symmetrical until airway smooth muscle constriction narrows the airway lumen to a critical level. Beyond this point, any small perturbation breaks the equilibrium and a small decrease in tidal volume to one branch reduces stretch to its walls, increasing smooth muscle forces and causing progressive airway narrowing. At the same time, the redistribution of flow to the other branch would cause it to dilate. It has been shown that airway interactions of this kind along the airway tree can lead to a highly heterogeneous response, and it is therefore conceivable that a small degree of heterogeneity in baseline ventilation can be greatly magnified during bronchoprovocation, increasing airway hyperactivity. This could explain why, in spite of a significant reduction in ventilation heterogeneity in the subjects treated with inhaled corticosteroid, the association of AHR with the post-treatment ventilation heterogeneity was virtually unchanged.

Even though AHR was correlated with FE\textsubscript{NO} in the baseline group of subjects, the puzzling question remains why such an association was not present in the treatment group before or after steroid treatment. Extensive experimental and modelling work has shown that exhaled nitric oxide originates both from airways and parenchyma, but the effect of ventilation heterogeneity on the FE\textsubscript{NO} signal remains unexplored. The lack of correlation between FE\textsubscript{NO} and AHR in the subgroup reportedly selected for having poorly controlled symptoms could in part have been the result of the increased heterogeneity in ventilation affecting the measurement of FE\textsubscript{NO}.

In summary, this elegant study shows that the indices of heterogeneity derived from the multiple breath nitrogen washout technique are strongly associated with AHR in asthma.
from the multiple breath nitrogen washout technique are strongly associated with AHR in asthma, and opens up a wide range of clinical and basic research avenues to elucidate the topographical and mechanistic basis of relationships between ventilation heterogeneity, exhaled nitric oxide analysis and AHR.

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REFERENCES


Staging of NSCLC

Evolution and science, progress and change

Frank C Dettterbeck

Positron emission tomography in staging of intrathoracic lymph nodes in non-small cell lung cancer

S taging of non-small cell lung cancer (NSCLC) has undergone a significant evolution, from plain chest radiographs to anatomical imaging, invasive techniques and, most recently, metabolic imaging using positron emission tomography (PET) scans. Even the literature regarding PET imaging has undergone significant evolution. Initial reports were characterised by compelling yet anecdotal images. This was followed by approximately 10 years of studies showing that mediastinal staging by PET was superior to computed tomography (CT) which, of course, was not surprising because CT had already been shown to be notoriously misleading in many situations. Eventually authors began addressing the clinically more relevant question of whether PET can replace invasive mediastinal staging. The article by Tournoy and colleagues1 in this issue of Thorax illustrates how far we have come (see page 696). Not only does this study use the most sophisticated technology—an integrated PET/CT scanner—but, more importantly, the authors have elevated the science a notch by thoughtfully evaluating nuances of scan interpretation in order to maximise what can be gained from this staging modality.

The overall scientific quality of the study by Tournoy and colleagues is good. An appropriate gold standard was used by requiring a surgical staging procedure after a negative needle staging test (transoesophageal ultrasound with needle aspiration, transbronchial needle aspiration, etc, which carry a 20–30% false negative rate).2 The authors should also be commended for looking at enlarged and normal size nodes separately, since PET uptake in smaller nodules is more difficult to detect. In addition, the careful evaluation of different objective criteria to try to improve the reliability of the PET interpretation is a valuable addition. On the other hand, reporting results on a per node basis statistically biases the results in favour of PET. Furthermore, this makes the data less applicable clinically because we must decide how to manage patients, not individual nodes. Additionally, lumping together mediastinal and hilar nodes biases the study in favour of PET because it avoids a distinction that can be difficult to make on PET. This also makes the data less clinically applicable because involved N1 nodes are generally treated differently from involved N2 nodes. An additional criticism is that the final assessment of the nodes is vague (which would also tend to bias the results in favour of PET).

It is unclear whether patients with a negative invasive staging went on to

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