

Multiple breath nitrogen washout profiles in asthmatic patients: What do they mean clinically?

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Mounting evidence over the years has clearly demonstrated abnormalities of structure and function in the lung periphery in asthmatic patients, involving both the small airways and the lung parenchyma.^{1,2} Although the anatomic evidence comes from tissue biopsy or postmortem studies, the functional evidence comes from both classic and novel means to probe the lung periphery, some of which are amenable to clinical implementation in our patients.^{1,2} This information leads to 2 important questions: What do these measurements mean, and what is their clinical significance?

Among the more clinically applicable methods to measure peripheral lung function is the inert gas washout technique.^{3,4} This method is used to assess ventilation heterogeneity and is the technique used by Thompson et al⁵ in their article in this issue of the *Journal*. This method can be applied by using the single-breath nitrogen washout technique to measure the phase III slope or the multiple-breath nitrogen washout (MBNW) technique to derive the convection (S_{cond})—and diffusion (S_{acin})—dependent indices of the phase III slope.^{3,4,6} S_{cond} is thought to reflect ventilation heterogeneity occurring in the conducting airways, where gas transport is driven by differences in pressure gradients and thus by convection. S_{acin} is thought to reflect ventilation heterogeneity occurring at and beyond the acinar region of the lung, where gas transport is driven by differences in concentration and thus by diffusion. Thus S_{cond} and S_{acin} values are sensitive to changes in the heterogeneity of ventilation at the “diffusion front,” which anatomically corresponds to the region of the acinus, at least in healthy lungs. Studies of S_{cond} and S_{acin} values have revealed a variety of interesting patterns that might relate to the specific contributions of the conducting versus acinar regions to asthma pathogenesis and treatment response (Table I).⁵⁻¹⁵

The current study by Thompson et al⁵ adds to this body of evidence by examining the relationship of peripheral lung function, as measured by using the MBNW technique, to the stability of asthma, as assessed by clinical presentation and use of asthma medications. Their article is unique because it studies peripheral

TABLE I. Summary of experimental findings relating ventilation heterogeneity in the conducting (S_{cond} value) and acinar (S_{acin} value) regions of the lung to various clinical features of asthma

Clinical feature	Abnormal S_{cond} values	Abnormal S_{acin} values	Reference
Stable (adults)	+	+	6
Stable (children)	+ (Trend)	—	7
Inflammation (exhaled nitric oxide)	—	+	8
Prediction of airways hyperresponsiveness	+	—	9
	+ (Younger)	+ (Older)	10
Response to methacholine	+	+	11
Response to bronchodilator	+ (Still abnormal)	++	12
Response to inhaled corticosteroids	+ (Larger particle)	++ (Addition of smaller particle)	13
	+ (Uptitration)	+ (Downtitration)	14
Asthma severity (FEV_1)	—	+	5
Asthma control	+	+	15
Acute exacerbation	++	+	5

+, Associated with clinical feature; ++, more strongly associated with clinical feature; —, not associated with clinical feature.

lung function in asthmatic patients presenting with a natural asthma exacerbation. The authors relate their findings to those from a population of patients with stable asthma and also examine the relationship between MBNW parameters and asthma severity, as determined by Global Initiative for Asthma (GINA) step level. Not surprisingly, the authors document that patients with an acute asthma exacerbation have worse lung function, as measured by lower FEV_1 and forced vital capacity values, but also show that they have higher S_{cond} values compared with those seen in patients with stable asthma. S_{acin} values were similarly abnormal in both groups compared with healthy control values. Interestingly, FEV_1 and GINA scores correlated with S_{acin} but not S_{cond} values, and S_{acin} values remained the sole contributing factor to FEV_1 in a multiple regression analysis. Finally, after 4 weeks of treatment following their exacerbation, FEV_1 , forced vital capacity, S_{cond} , and S_{acin} values all improved, most into the range of the stable asthma group. The authors conclude that unstable asthma is characterized by abnormalities in both the conducting and acinar lung zones, which are improved with therapy, but only the acinar component correlates with FEV_1 and treatment requirements, as determined by GINA step. They speculate that both the conducting and acinar regions are abnormal in asthmatic patients because of variable contributions of inflammation and remodeling, with the acinar compartment (ie, the lung periphery beyond the small conducting airways) particularly contributing to asthma severity and the treatment requirement for any individual patient.

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This was a well-done study by a group with special expertise in the MBNW technique. Although their discussion of the results seems reasonable, there are a few limitations to their conclusions. First, the authors do not discuss the finding on presentation that there was a significant difference in S_{cond} values between the unstable and stable groups. It is tempting to speculate that although the acinar region is likely involved in asthma pathogenesis, acute exacerbations might be associated with abrupt changes in the conducting airways (ie, severe heterogeneous narrowing by airway smooth muscle constriction or inflammation/edema/mucus obstruction). Second, it does not seem reasonable to use the GINA step level at presentation to represent asthma severity because the patients who presented with an asthma exacerbation had severe asthma by definition, regardless of their GINA step level. It is possible that some patients with acute exacerbation were undertreated and some with stable asthma were overtreated. In fact, all but 1 of the patients with stable asthma had GINA step 3 or 4 levels, and many unstable patients had GINA step 1 or 2 levels. Although the authors admit that the GINA step might have underestimated the level of severity, for this reason it is difficult to relate acinar involvement with asthma severity based on treatment requirements.

A general limitation to the study is that all testing was done by necessity at some point after presentation among the patients with an acute exacerbation, and thus the findings likely underestimate the severity of lung dysfunction at the time of presentation. This might explain why there was no apparent difference in S_{acin} values between the acute exacerbation group and the stable group because peripheral airway function might improve earlier or be more amenable to acute therapy than more central airway function. This is an inherent limitation of studying patients under conditions of an acute exacerbation, and the authors are to be commended for carrying out this challenging type of study.

Another general limitation relates to the interpretation of results. As with all studies that use the MBNW technique, understanding the underlying anatomic correlates of the findings is dependent on the computational modeling used to analyze the results. Because modeling was derived from the anatomy and function of healthy lungs, it is unclear how the results should be interpreted in the context of the abnormal lung in asthmatic patients.⁴ Thus although one can conclude that there are abnormalities in S_{acin} values, it is not certain whether these abnormalities directly relate to the lung periphery. As suggested by Verbanck et al,¹⁶ an interaction between S_{acin} and S_{cond} values seen in asthmatic patients might result from heterogeneous airway constriction in the proximal airway tree extending to the peripheral bronchioles. Perhaps it is even possible that the diffusion front could move proximally if larger airway narrowing limits flow sufficiently to create conditions suitable to ventilation by diffusion (ie, lower flow rates) distal to the narrowing. Indeed, in the presence of severe ventilation heterogeneity, as might be expected during an acute asthma exacerbation (unstable group), S_{acin} values might not be accurate.^{3,4}

Interpreting the clinical significance of the patterns of abnormality of S_{cond} and S_{acin} values according to current findings (Table I) is challenging. It appears that heterogeneity of conducting airway ventilation (S_{cond} value) is associated with airway hyperresponsiveness, acute exacerbation, and airway remodeling, whereas heterogeneity of acinar airway ventilation (S_{acin} value) is more associated with asthma severity and inflammation. Asthma control and response to therapy seem to involve both types of ventilation heterogeneity. Combining the MBNW technique with other methods, such as the forced oscillation technique¹¹ or imaging studies,¹⁷ could provide complementary information that will yield more specific insight into anatomic and functional abnormalities of the lung periphery in asthmatic patients. In this way the MBNW test might become a useful tool to predict asthma control and help guide therapy to optimize asthma care.

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