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Predictors of Airway Hyperresponsiveness Differ Between Old and Young Patients With Asthma

Kate M. Hardaker, BSc; Sue R. Downie, PhD; Jessica A. Kermode, BSc (Hons1); Claude S. Farah, MBBS; Nathan J. Brown, PhD; Norbert Berend, MD, FCCP; Gregory G. King, PhD; and Cheryl M. Salome, PhD

Background: Age-related increases in morbidity and mortality due to asthma may be due to changes in pathophysiology as patients with asthma get older. There is limited knowledge about the effects of age on the predictors of airway hyperresponsiveness (AHR), a key feature of asthma. The aim of this study was to determine if the pathophysiologic predictors of AHR, including inflammation, ventilation heterogeneity, and airway closure, differed between young and old patients with asthma.

Methods: Sixty-one young (18-46 years) and 43 old (50-80 years) patients with asthma had lung function, lung volumes, fraction of exhaled nitric oxide, ventilation heterogeneity, and airway responsiveness to methacholine measured. Airway response to methacholine was measured by the dose-response slope, as the percent fall in FEV₁ per micromole of methacholine. Indices of ventilation heterogeneity were calculated for convection-dependent and diffusion-dependent airways.

Results: In young patients with asthma, the independent predictors of AHR were convection-dependent ventilation heterogeneity, exhaled nitric oxide, and % predicted FEV₁/FVC (model $r^2 = 0.51$, $P < .0001$). In old patients with asthma, the independent predictors of airway responsiveness were % predicted residual volume, diffusion-dependent ventilation heterogeneity, and % predicted FEV₁ (model $r^2 = 0.57$, $P < .0001$).

Conclusions: In old patients with asthma, AHR is predicted by gas trapping and ventilation heterogeneity in peripheral, diffusion-dependent airways. In the young, it is predicted by ventilation heterogeneity in less peripheral conducting airways and by inflammation. These findings suggest that there are differences in the pathophysiologic determinants of AHR between young and old patients with asthma.

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Abbreviations: ACQ = Asthma Control Questionnaire; AHR = airway hyperresponsiveness; DRS = dose-response slope; FENO = fraction of nitric oxide in exhaled breath; ICS = inhaled corticosteroid; ppb = parts per billion; RV = residual volume; Sacin = ventilation heterogeneity in diffusion-dependent airways; Scand = ventilation heterogeneity in convection-dependent airways

Increasing age is associated with worse asthma control,¹ and mortality due to asthma increases sharply after age 65 years.² The reasons behind the age-related changes in clinical outcomes of asthma are unclear, and may be related to comorbidities in older patients, differing psychosocial circumstances, or physiologic changes associated with aging. The normal aging process leads to decreased lung function,³ decreased lung elastic recoil,⁴ and an altered expression of inflammatory cells.⁵ However, very few studies have examined the effect of these age-related changes on the pathophysiology of asthma in the elderly. If aging

has independent effects on the pathophysiology of asthma, then the clinical expression of disease and its response to treatment will be different in old compared with young patients with asthma. It is, therefore, essential to establish whether the pathophysiologic processes associated with asthma in older patients differ from those in young patients with asthma.

Airway hyperresponsiveness (AHR), a fundamental pathophysiologic characteristic of asthma, is correlated with many clinical features, which include increased decline in FEV₁,⁶ and increased risk of exacerbations.⁷ AHR is predicted by sputum eosinophils,⁸

fraction of nitric oxide in exhaled breath (FENO),^{8,9} heterogeneous distribution of ventilation,⁹ and airway closure.¹⁰ Little is known about the effects of age on the clinical outcomes or pathophysiologic predictors of AHR. Age-related changes in the inflammatory profile in asthma suggest that the role of eosinophilic inflammation as a driver of AHR may be less important as patients age. Neutrophilic inflammation increases in older patients with asthma¹¹ and eosinophilic cell function changes as patients get older.¹² Ventilation heterogeneity also changes with age, increasing dramatically at around 50 years of age.¹³ Lung function is reduced in older patients with asthma, which may be due to increased airway remodeling as a result of longer duration of disease and also to the loss of lung elastic recoil. Such impairments may also lead to greater lung hyperinflation and airway closure, the latter being associated with more severe AHR¹⁰ and severe disease.¹⁴

We hypothesized that AHR is determined by different pathophysiologic processes in old compared with young adults with asthma. We propose that as the inflammatory profile and airway mechanical properties alter with age, other pathophysiologic processes, such as increased ventilation heterogeneity and airway closure, assume greater importance in predicting AHR. The aim of this study was to determine the predictors of AHR in old patients with asthma and to compare these with the predictors in young patients with asthma.

MATERIALS AND METHODS

Subjects

Subjects were recruited by advertising throughout The University of Sydney and from the volunteer database at the Woolcock Institute of Medical Research. Inclusion criteria were physician diagnosis of asthma plus current symptoms of asthma requiring regular treatment. Subjects were excluded if they had smoked

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Affiliations: From the Woolcock Institute of Medical Research (Mss Hardaker and Kermodé and Drs Downie, Farah, Brown, Berend, King, and Salomé), Glebe; The University of Sydney, Sydney (Mss Hardaker and Kermodé and Drs Downie, Farah, Brown, Berend, King, and Salomé); the Cooperative Research Centre for Asthma and Airways (Mss Hardaker and Kermodé and Drs Downie, Farah, Brown, Berend, King, and Salomé), Glebe; and the Department of Respiratory Medicine (Dr King), Royal North Shore Hospital, St Leonards, NSW, Australia.

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Correspondence to: Kate Hardaker, BSc, Woolcock Institute of Medical Research, PO Box M77, Missenden Rd, Glebe, NSW, 2050, Australia; e-mail: kateh@woolcock.org.au

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within the last 6 months, had a smoking history ≥ 10 pack-years, had any major respiratory disease other than asthma, had a respiratory tract infection, or used oral prednisone in the previous 4 weeks. Written informed consent was obtained from all subjects, and the study was approved by the Human Research Ethics Committee of the South-Western Sydney Area Health Service (protocol number X06-0046).

Study Design

This was a cross-sectional study in which all data were collected in a single visit. Short- and long-acting β_2 -agonists were withheld for 6 h and 24 h before testing, respectively. Subjects completed a questionnaire about medication use, disease duration, and smoking history, and the Asthma Control Questionnaire (ACQ).¹⁵ Subjects with ACQ scores < 0.75 were classified as well controlled, between 0.75 and 1.5 as intermediately controlled, and scores ≥ 1.5 were classified as poorly controlled.¹⁶ Atopic status was determined by skin prick test to common aeroallergens.

Exhaled Nitric Oxide

FENO was measured as an indirect marker of airway inflammation. It was measured using an off-line technique according to American Thoracic Society guidelines.¹⁷ Subjects inhaled room air through a nitric oxide scrubber and exhaled against a small resistance into a nitric oxide-impermeable polyethylene bag (Scholle Industries Pty Ltd; Elizabeth West, South Australia, Australia) at a constant flow of 0.2 L/s. The exhaled gas was analyzed using a chemiluminescence analyzer (model 42C; Thermo Environmental Instruments Inc; Franklin, Massachusetts). The upper limit of normal FENO_{0.2} in adults is 13 parts per billion (ppb).¹⁸

Spirometry and Plethysmography

Spirometry and plethysmography were performed using a SensorMedics Vmax spirometer (SensorMedics Corp; Yorba Linda, California) and a Medisoft BodyBox 5500 (Medisoft Corp; Sorries, Belgium). Results were reported as percent predicted.^{3,19}

Ventilation Heterogeneity

Ventilation heterogeneity was measured by the multiple-breath nitrogen washout as previously described.⁹ Briefly, a closed-circuit, bag-in-box breathing system was used to deliver 100% oxygen, which subjects breathed at a tidal volume of 1.0 to 1.3 L, until end-tidal nitrogen concentration dropped to 1/40 of the starting alveolar nitrogen concentration. The indices of ventilation heterogeneity in the regions of the lung where gas transport occurs predominantly by convection (Scond) and by diffusion (Sacin) were derived as previously described.²⁰

Methacholine Challenge

Methacholine challenge tests were performed using hand-held De Vilbiss No 45 nebulizers (Sunrise Medical; Carlsbad, California), with doses ranging from 0.05 μmol to 6.1 μmol using the rapid method.²¹ Response to challenge was measured by the dose-response slope (DRS), which is calculated as $([\% \text{ fall in FEV}_1/\mu\text{mol methacholine}] + 3)$.²² AHR was defined as $\text{DRS} > 8\%$ fall in FEV₁/ μmol (equivalent to FEV₁ provocative dose causing a 20% reduction in FEV₁ $< 4 \mu\text{mol}$).

Statistical Analysis

Data were analyzed using the Analyze-It software for Microsoft Excel (Analyze-It Software Ltd; Leeds, England). DRS and

FENO were log-normally distributed and were \log_{10} transformed for all analyses. Because ventilation heterogeneity increases sharply at 50 years of age,¹³ subjects were classified into two age groups: young (<50 years) and old (≥ 50 years). Testing of interactions between age group and each of the independent variables showed significant interactions between age group and FENO, and age group and Scnd. Therefore, the univariate and multivariate associations between DRS and the predictor variables were analyzed separately for each age group. Separate backward, stepwise, multiple linear regressions were conducted to determine the predictors of logDRS in old and young patients with asthma and included the following factors: Scnd, Sacin, FENO, % predicted FEV₁, % predicted FVC, % predicted FEV₁/FVC, % predicted residual volume (RV), and BMI. Data are presented as means with 95% CIs unless otherwise specified. *P* values < .05 were considered statistically significant.

RESULTS

Subjects

One hundred four subjects with asthma participated in the study. Table 1 shows the characteristics of subjects in the young and old groups. The prevalence of AHR was lower in the old group (49%) than in the young group (70%, *P* = .03). Compared with young patients with asthma, the old patients with asthma had longer disease duration, more airflow obstruction, less severe AHR, and lower FENO. Diffusion-dependent ventilation heterogeneity (Sacin) was worse in the old group than in the young group, whereas convection-dependent ventilation heterogeneity (Scnd) was similar. The old group tended to be

less atopic, but this was not statistically significant. More old patients with asthma were receiving regular inhaled corticosteroid (ICS) treatment than young patients with asthma; however, in those taking ICSs, dosages were comparable between the groups. The number of subjects in each asthma control (ACQ) classification was similar in the old and young. Smoking history was negligible, as there were only seven ex-smokers in total (five old and two young), with median (interquartile range) smoking history of 5 (2-8) pack-years.

Univariate Correlations With DRS

In both old and young patients with asthma, DRS correlated negatively with % predicted FEV₁ and % predicted FEV₁/FVC and positively with % predicted RV (Table 2). DRS correlated with FENO in the young but not in the old group. DRS positively correlated with Sacin in the old and with Scnd in the young (Fig 1). DRS was a significant predictor of asthma control, measured by ACQ in both old (*r* = 0.62, *P* < .0001) and young (*r* = 0.42, *P* < .001) patients with asthma.

Multivariate Correlations With DRS

Table 3 shows the results of the multiple linear regression analyses. In the old group, the independent predictors of DRS were % predicted RV, Sacin, and % predicted FEV₁ (model *r*² = 0.57, *P* < .0001). In the young group, DRS was independently predicted

Table 1—Characteristics of Study Subjects

Characteristic	Young	Old	<i>P</i> Value
No. (male)	61 (31)	43 (22)	.9
Mean age (range), y	28 (18-46)	59 (50-80)	...
Disease duration, y	21.3 (19.3-23.2)	35.5 (30.0-41.1)	< .0001
BMI, kg/m ²	25.5 (24.1-26.8)	26.8 (25.4-28.1)	.2
Well controlled, No. (%)	21 (34)	17 (41)	.5
Intermediately controlled, No. (%)	23 (38)	15 (37)	.9
Poorly controlled, No. (%)	17 (28)	9 (22)	.8
Atopic, No. (%)	60 (98)	39 (91)	.07
FENO, ppb ^a	14.7 (13.5-15.9)	9.9 (8.7-11.1)	.003
Scnd/L	0.058 (0.050-0.067)	0.063 (0.054-0.071)	.5
Sacin/L	0.124 (0.109-0.140)	0.185 (0.161-0.209)	< .0001
DRS, % fall FEV ₁ /μmol methacholine + 3 ^a	23.2 (21.8-24.6)	9.8 (8.5-11.2)	< .001
FEV ₁ , % pred	77.9 (74.3-81.5)	75.4 (70.9-79.8)	.4
FVC, % pred	91.1 (88.2-94.0)	90.4 (86.3-94.5)	.8
FEV ₁ /FVC, % pred	83.0 (79.7-86.4)	77.5 (73.8-81.1)	.03
TLC, % pred	111.2 (106.3-116.2)	105.9 (98.5-113.5)	.2
FRC, % pred	103.7 (97.1-110.4)	112.7 (106.7-118.7)	.07
RV, % pred	139.0 (129.7-148.4)	130.1 (122.2-138.0)	.2
Taking ICS, No. (%)	34 (56)	37 (86)	< .001
BDP equivalent dose, μg/d	778 (545-1012)	758 (589-927)	.9

Values are mean (95% CI) unless otherwise stated. BDP = beclomethasone dipropionate; DRS = dose-response slope; FENO = fraction of nitric oxide in exhaled breath; FRC = functional residual capacity; ICS = inhaled corticosteroid; ppb = parts per billion; pred = predicted; RV = residual volume; Sacin = ventilation heterogeneity in diffusion-dependent airways; Scnd = ventilation heterogeneity in the convection-dependent airways; TLC = total lung capacity.

^aGeometric mean (95% CI).

Table 2—Univariate (Pearson) Correlations Between Predictor Variables and Airway Responsiveness

DRS	Young		Old	
	<i>r</i>	<i>P</i> Value	<i>r</i>	<i>P</i> Value
FENO, ppb	0.41	.001	0.03	.9
Scnd/L	0.54	<.0001	0.29	.06
Sacin/L	0.17	.2	0.47	.002
FEV ₁ , % pred	-0.54	<.0001	-0.57	<.0001
FEV ₁ /FVC, % pred	-0.57	<.0001	-0.52	<.001
RV, % pred	0.34	.007	0.59	<.0001

See Table 1 legend for expansion of abbreviations.

by Scnd, FENO, and % predicted FEV₁/FVC (model $r^2 = 0.51$, $P < .0001$). When subjects without AHR (DRS < 8% fall FEV₁/μmol) were excluded, DRS was 33.4 (21.5-45.3) % fall FEV₁/μmol in the old and 77.9 (51.9-103.9) % fall FEV₁/μmol in the young group ($P = .02$). The multivariate predictors of AHR in the old group with AHR did not change (model $r^2 = 0.50$, $P = .002$) and in the young group with AHR were Scnd and % predicted FEV₁/FVC (model $r^2 = 0.26$, $P = .002$).

To determine if the differences between young and old groups were a reflection of differences in ICS use, the data were reanalyzed after limiting the data set to subjects currently taking regular ICS therapy. In this subset, there were no significant differences in FENO between old and young patients with asthma

(10.3 [8.7-12.2] ppb vs 12.8 [9.9-16.3] ppb, respectively, $P = .2$); however, DRS was lower compared with younger patients with asthma (10.2 [7.3-14.2] % fall FEV₁/μmol vs 27.5 [16.4-46.2] % fall FEV₁/μmol, $P = .002$). The multivariate predictors of DRS in this subgroup were the same as for the group as a whole for both old (model $r^2 = 0.63$, $P < .0001$) and young (model $r^2 = 0.50$, $P < .0001$) patients with asthma.

DISCUSSION

In this study of young (18-46 years) and old (≥ 50 years) adults with asthma, we found differences in the pathophysiologic determinants of AHR. The presence of significant interactions between age group and key predictor variables implied that there were significant qualitative differences between age groups in their relationship with AHR, which made it essential to analyze the two groups separately. In old patients with asthma, AHR was predicted by gas trapping (% predicted RV), Sacin, and airway obstruction (% predicted FEV₁). In young patients with asthma, AHR was predicted by airway obstruction (% predicted FEV₁/FVC), FENO, and Scnd. The important health burden of asthma in the elderly was recognized in a recent review by Braman,²³ who suggested that the clinical presentation of asthma is similar in young and old and that AHR and atopy are

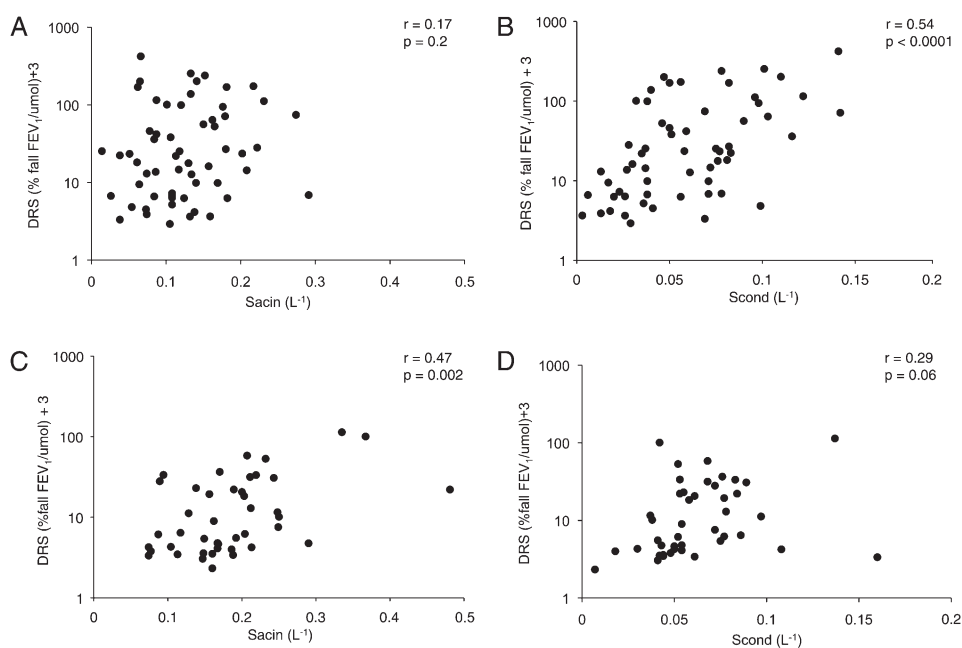


FIGURE 1. The relationship between airway responsiveness (DRS) and ventilation heterogeneity in young and old patients with asthma. **A**, Sacin does not correlate with DRS in young patients with asthma. **B**, Scnd correlates with DRS in young patients with asthma. **C**, Sacin correlates with DRS in old patients with asthma. **D**, Scnd does not correlate with DRS in old patients with asthma. DRS = dose-response slope; Sacin = ventilation heterogeneity in diffusion-dependent airways; Scnd = ventilation heterogeneity in convection-dependent airways.

Table 3—Results of Multiple Linear Regression Analyses to Predict Airway Responsiveness

Age Group	Predictor	β Coefficient (SE)	Partial r^2	Model r^2	P Value
Young	FEV ₁ /FVC, % pred	-0.018 (0.005)	0.32
	FENO, ppb	0.658 (0.18)	0.12
	Scond/L	5.352 (1.86)	0.07	0.51	<.0001
Old	RV, % pred	0.008 (0.004)	0.33
	Sacin/L	1.932 (0.002)	0.19
	FEV ₁ , % pred	-0.009 (0.62)	0.05	0.57	<.0001

All predictors remaining in the model were significant at $P < .05$. See Table 1 legend for expansion of abbreviations.

important features of asthma at all ages. Our findings are consistent with this view, and we found that AHR is a significant predictor of asthma control in both young and old patients with asthma. However, the differences in the pathophysiology suggest that AHR in old patients with asthma is related to disease processes that occur in small, peripheral airways.

The patients included in this study had asthma diagnosed by a physician and were currently taking treatment of asthma consistent with the definition used in recent large clinical trials.²⁴ Subjects were not required to have AHR, because AHR to methacholine is not specific for asthma and because responsiveness can be reduced into the nonresponsive range by treatment with ICS.²⁵ The inclusion of subjects without AHR meant that the sample included a wide spectrum of subjects with asthma from mild, well-treated subjects to untreated or severe disease. It is unlikely that the old group included a significant proportion with COPD because smoking history in both groups was negligible. One of the strengths of this study was the use of the DRS, which is a continuous measure of the severity of airway responsiveness. This allowed the predictors of airway responsiveness to be determined across the whole range of responses in the sample, without relying on the arbitrary definition of AHR. It is noteworthy that when the analysis was limited to those subjects with AHR, the predictors of the severity of AHR in the old group were unchanged. However in the young group, FENO was no longer a predictor of AHR, suggesting that high FENO predicts the presence, but not the severity, of AHR.

The results of the current study show that the relationship between AHR and airway inflammation differs in old and young patients with asthma. Airway inflammation, measured directly by sputum inflammatory cells or indirectly by FENO, is a well-established predictor of AHR,^{8,9} which is consistent with our findings in young patients with asthma. In the current study, FENO in old patients with asthma was within normal limits,¹⁸ which may be due to the large proportion of the group on ICS treatment. In the subset of subjects taking regular inhaled ICSs, FENO was similar in old and young; however, DRS

correlated with FENO in only the young patients with asthma. This suggests that the between-group difference in the contribution of airway inflammation to AHR was not due to differences in treatment. Alternatively, low FENO and the lack of association between FENO and AHR in old patients with asthma may be a result of different inflammatory profiles in old and young patients with asthma. Sputum neutrophils are known to increase with age; however, there is little change in eosinophils.¹¹ Sputum was not collected in the present study, so we were unable to determine the inflammatory subtypes of the subjects. However, previous studies have shown that FENO correlates well with sputum eosinophils.⁸ Thus, the absence of any association between AHR and FENO in the old patients with asthma suggests that eosinophilic airway inflammation is not an important determinant of AHR in this group. Cluster analysis studies have shown that airway inflammation, airway obstruction, and AHR belong to different clusters in asthma models.²⁶ The observation that inflammation (FENO) is a strong predictor of AHR in young, but not in old, patients with asthma could suggest that the dominant clusters that determine asthma phenotype differ in old and young patients with asthma.

Disease duration may also play a role in the pathophysiology of AHR. In a previous study of relatively young adults, inflammation was associated with AHR in subjects with short (≤ 16 years) but not with long (> 16 years) duration of asthma.²⁷ In older patients with asthma, chronic inflammation associated with longstanding disease increases remodeling in the airways.²⁸ In the current study, duration of disease was much longer in the old group than in the young group, as expected, but there was no association between AHR and disease duration in either group. This suggests that, in these subjects, there are no additional, independent effects of disease duration on AHR after accounting for age. The cross-sectional design of the study allowed us to determine if the predictors of AHR differed between old and young patients with asthma, but it did not allow us to distinguish between the effects of aging and longstanding disease.

Spirometric measures of airway obstruction were significant predictors of DRS independent of age, which is consistent with previous studies.^{10,22} The association between baseline airway caliber and AHR is often explained in terms of a geometric effect, whereby bronchoconstriction has a much greater effect on airways with small starting caliber than on those with larger caliber.^{29,30} Baseline airway caliber can be reduced by disease- and age-related factors, which include loss of lung elastic recoil, airway wall remodeling, inflammation, and changes in surface active forces. These factors may also increase ventilation heterogeneity. In the present study, airway caliber was adjusted for age by using the percent predicted values in the regression models, and the association between baseline airway caliber and AHR was independent of ventilation heterogeneity.

In the current study, AHR was predicted by Sacin in old patients with asthma. Because Sacin reflects ventilation heterogeneity in diffusion-dependent airways, rather than in the convection-dependent airways reflected by Scond, this finding suggests that AHR in old patients with asthma involves very peripheral airways. It is unknown whether the anatomic boundaries of Scond and Sacin change with age or disease. In the present study, Sacin was greater in the old patients with asthma than in the young; however, it is unclear whether this was due to aging itself or to disease processes. In healthy adults, ventilation heterogeneity increases with age since both the lung clearance index and the phase 3 slope of the single-breath nitrogen washout increase sharply after 50 years of age.^{13,31} However, to our knowledge, there are no published data about the effect of aging on Sacin. In the current study, multivariate analysis in the old group showed that age was not an independent predictor of AHR, suggesting that the relationship between AHR and Sacin in old subjects was due to disease rather than the aging process. The precise mechanisms by which increased ventilation heterogeneity contributes to AHR are unknown; however, computational modeling predicts that in the presence of uniform airway smooth muscle activation, increased ventilation heterogeneity may lead to large-scale but localized regions of airway closure.³²

Baseline airway closure, measured by RV, was a significant predictor of AHR in the old, but not the young, patients with asthma in the present study. Old patients with asthma are at increased risk of airway closure, measured by the change in FVC during bronchial challenge,³³ but it is not known whether subjects who are predisposed to increased airway closure during challenge are more likely to have gas trapping at baseline. Irvin and Bates³⁴ proposed that airway closure is central to AHR in asthma, and that

the closure-related increase in RV is accompanied by an increase in total lung capacity. Old subjects with peripheral airway abnormalities that predispose the subject to airway closure may be at particular risk if they also have elevated baseline RV or total lung capacity, since any additional airway closure during challenge would bring them closer to the limit of chest wall expansion. Airway closure is a clinically important feature of asthma, since it is a significant predictor of the severity of AHR¹⁰ and is a risk factor for severe asthma exacerbations.¹⁴

In this study we found that the pathophysiologic processes that determine AHR in old patients with asthma differ from those in the young. Specifically, our results show that AHR in old patients with asthma is determined by abnormalities in peripheral airways. The clinical implications of this finding are that gas-trapped and diffusion-dependent areas of the lung in old patients with asthma may not respond well to conventional inhaled medications. These findings suggest that, to reduce morbidity and mortality in old patients with asthma, different systemic treatments may be required to effectively target peripheral airways where airway closure and gas trapping occur. Further studies will be needed to better understand the mechanisms that underlie AHR in the elderly and determine the separate effects of disease and aging on AHR.

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Author contributions: Ms Hardaker and Dr Salome had access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ms Hardaker: contributed to the implementation, statistical analysis, interpretation, and writing.

Dr Downie: contributed to the design, implementation, interpretation, and writing.

Ms Kermode: contributed to the implementation, interpretation, and writing.

Dr Farah: contributed to the implementation, interpretation, and writing.

Dr Brown: contributed to the design, statistical analysis, interpretation, and writing.

Dr Berend: Contributed to the design, interpretation, and writing.

Dr King: contributed to the design, statistical analysis, interpretation, and writing.

Dr Salome: contributed to the design, implementation, statistical analysis, interpretation, and writing.

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