

Chronic hyperplastic eosinophilic sinusitis as a predictor of aspirin-exacerbated respiratory disease

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Background: Aspirin-exacerbated respiratory disease (AERD) is a disease of intense eosinophilic inflammation that can produce fibrosis, hyperplasia, and remodeling.

Objective: To investigate the usefulness of quantifying severity of chronic hyperplastic eosinophilic sinusitis in predicting the presence of AERD.

Methods: Data were compared between asthmatic patients who reported exacerbations after aspirin ingestion and those who did not. The primary outcome measure was severity of sinusitis using a validated computed tomography (CT) scan–based scoring system. Indices of lower airway remodeling and other markers of inflammation were also evaluated.

Results: Twenty-one patients with AERD were compared with 19 patients with aspirin-tolerant asthma (ATA). Patients were well matched for asthma severity as shown by their similar lung function as measured by postbronchodilator forced expiratory volume in 1 second. Patients with AERD were distinguished by their sinus CT scores (AERD patients: 16.9; 95% confidence interval [CI], 13.4–21.3; ATA patients: 6.2; 95% CI, 4.2–9.1; $P < .001$), and they were considerably more likely to have nasal polyps (AERD patients: 90%; ATA patients: 26%; $P < .001$). In addition, AERD patients demonstrated increased total lung capacity (AERD patients: 107.9%; 95% CI, 99.9%–117.6%; ATA patients: 98.0%; 95% CI, 93.7%–102.5%; $P = .05$), reflecting a trend toward increased air trapping. No significant differences occurred in diffusing capacity, exhaled nitric oxide, eosinophilia, or exhaled breath condensate pH.

Conclusions: AERD can be distinguished from ATA by the extent of hyperplasia on CT scan and the presence of nasal polyps. We hypothesize that AERD represents a remodeling process that affects both the upper and lower airways.

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INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is characterized by the triad of nasal polyps, aspirin sensitivity, and asthma. Additional features of this disorder are its association with chronic hyperplastic eosinophilic sinusitis (CHES), tissue and circulating eosinophilia, and the frequent absence of atopy.^{1–3} Aspirin intolerance may occur in as many as 20% of adult asthmatic patients and up to 30% of asthmatic patients with CHES or nasal polyposis (NP).^{2,4} Patients typically present in the third decade with a variable degree of intense rhinitis, facial flushing, and nasal congestion after exposure to aspirin or other nonspecific cyclooxygenase (COX) inhibitors. Subsequently, patients develop the full spectrum of the disorder, including presence of nasal polyps, anosmia, and

asthma.^{5,6} In many patients, asthma does not develop, thus the current preference for the term *AERD* rather than *aspirin-intolerant asthma* or *triad asthma*.

The nasal polyp and sinus pathology of AERD is associated with an intense infiltration of eosinophils and evidence for eosinophilic activation as shown through release of eosinophil granule contents such as major basic protein or eosinophil cationic protein.^{7–9} CHES/NP with or without aspirin intolerance is also characterized by the presence of numerous activated lymphocytes, goblet cells, mast cells, and fibroblasts.^{8,10,11} These activated immune cells demonstrate increased production of cytokines associated with eosinophilic inflammation.^{10–14} The fact that eosinophils are one prominent source of these cytokines suggests that CHES or NP is a disease in part of dysregulated self-perpetuating inflammation. CHES (with or without aspirin intolerance) is frequently associated with asthma. As many as 74% to 90% of patients with asthma demonstrate sinus computed tomography (CT) abnormalities.^{15–18} The presence of CHES both correlates with and is thought to contribute to asthma severity. Thus, patients with more severe CHES were shown to have asthma that was associated with a higher morbidity and worse prognosis when compared with patients with mild disease.^{15,18} Interestingly, in this latter study,¹⁸ severity of CHES also correlated with evidence for asthma remodeling

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as shown by increased residual volume and diminished diffusing capacity. Both this correlation of lower airway remodeling with severity of sinusitis and the similarities in the pathologic features of these 2 disorders suggest that CHES and asthma are similar pathologic processes in the upper and lower airways, respectively.

We recently published details of our experience regarding the usefulness of the CT scan in distinguishing patients with vocal cord dysfunction from those with asthma.¹⁹ Although also producing intermittent airflow obstruction, vocal cord dysfunction is contrasted with asthma by the absence of inflammation. In this study, patients with vocal cord dysfunction did not display inflammatory changes on their sinus CT examinations. It was noteworthy that the 6 patients with the worst sinusitis scores on their CT scans all reported the presence of AERD, and this finding instigated the current study. Similarly, although the study by ten Brinke et al¹⁸ did not rigorously address the presence of aspirin intolerance in their severe CHES cohort, this was present in 4 of 5 patients with the worst CT scores in whom these data were available. We therefore speculated that CHES would be more severe in AERD and that this severity could be used to predict the presence of aspirin intolerance. Although the prevalence of NP in this disorder has been assumed to reflect a manifestation of severe sinusitis, quantification of the extent of sinusitis using validated criteria has never been addressed in this disorder. The current studies used the sinus CT to determine its efficacy in distinguishing AERD from aspirin-tolerant asthma (ATA). In addition, we compared other clinical markers of inflammation between these 2 cohorts, including presence of nasal polyps, exhaled breath nitric oxide (NO) and condensate pH, absolute eosinophil counts, IgE, and physiologic markers of lower airway remodeling, including lung volume, spirometry, and diffusing capacity.

MATERIALS AND METHODS

Study Design and Participants

Twenty-one patients with AERD were prospectively compared with 19 patients with ATA at University of Virginia Health System facilities. Informed consent was obtained from all patients before enrollment under a protocol approved by the institutional review board. Entrance criteria required patients to be between the ages of 18 and 60 years with prior exposure to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), to have controlled asthma in the absence of other cardiopulmonary disease, and to have a less than 5-pack-year history of tobacco use. Patients with ATA were matched for severity of their asthma based on previously established criteria.²⁰ All patients with known AERD who met the inclusion criteria were contacted and, if they agreed to participate, enrolled. Sources of ATA patients included the Clinical Data Repository, the Allergy and Immunology Clinic, and the Pulmonary Clinic at the University of Virginia. Patients were only evaluated during one session to prevent dropouts. An asthma questionnaire was used to obtain a detailed history of

medication use, asthma severity and duration, allergic rhinitis, and nasal polyps, as well as a detailed history regarding exposure to aspirin and other NSAIDs. Presence and extent of NP were evaluated by rhinoscopy. Patients with AERD gave an unambiguous history of a severe asthma exacerbation that occurred within 2 to 3 hours of ingestion of aspirin or other NSAIDs.

Inflammatory Markers

Absolute circulating eosinophil concentrations and total IgE levels were evaluated in the clinical laboratory with standard techniques. Exhaled breath NO samples were collected as previously described, using techniques shown to exclude upper airway-derived NO.¹⁹ Measurement of pH was performed on exhaled breath condensates with a glass microelectrode, after carbon dioxide extraction via bubbling the sample with argon at 350 mL/min until the pH reading was stable, as previously described.²¹

Pulmonary function was evaluated using spirometry, plethysmography, and diffusing capacity of lung for carbon monoxide (DLCO). Spirometry was evaluated before and 15 minutes after administration of albuterol.

Sinus disease was evaluated using a noncontrast coronal helical CT scan. All CT scans were assigned a quantitative score by a blinded investigator according to our previously published and validated methods.^{15,19,22,23}

Statistical Analysis

Patient baseline characteristics and the demographic variables that were summarized as frequencies were compared between the ATA and AERD patients with a binomial-exact test. The age distribution of the patients and the patients' asthma history (duration) were compared using the Wilcoxon non-parametric rank sum test. One-way analysis of variance (ANOVA) was used to compare the inflammatory markers (CT score, eosinophils, IgE, exhaled NO, and pH) and the pulmonary function parameters between the ATA and AERD patients. To comply with the normality and the equal variance assumptions of the 1-way ANOVA, the inflammatory marker data and the pulmonary function data were analyzed on the natural logarithmic scale. The estimates for the means and difference between the means that were obtained from the ANOVA were transformed back to the original scale by antilogarithmic transformation. The between-group comparisons made between the ATA and AERD patients were therefore summarized as geometric means. Logistic regression was used to derive an equation for predicting the probability of AERD as a function of the patient's CT score. Figure 2 was generated with an inverse transformation, in which the predicted logit and the 95% confidence interval were transformed from the logit scale to the probability scale.

RESULTS

Population Demographics

Patients with ATA and those with AERD were well matched in terms of age, race, allergic rhinitis, asthma control, and use

of high-dose inhaled steroids (Table 1). Asthma duration was shorter in the AERD cohort ($P = .28$). There were slightly more female ATA patients than AERD patients (79% vs 52%, $P = .21$). Leukotriene modifiers were also used more frequently by asthmatic patients with AERD (67% vs 40%, $P = .27$).

Pulmonary Function

The 2 cohorts were well matched in terms of asthma severity as shown by their similar spirometry results (Table 2). However, AERD patients demonstrated significantly increased total lung capacity. This increase in total lung capacity may have reflected increased air trapping as shown by the trend toward elevated residual volume.

Sinus CT and Nasal Polyps

Severe sinus disease (CT score ≥ 12) was present in 5 (26%) of 19 control patients and 17 (81%) of 21 AERD patients ($P = .001$) (Fig 1). Patients with AERD had significantly more severe sinusitis based on sinus CT score (16.9 vs 6.2; $P < .001$; Table 3), and probability of AERD may be predicted based on sinus CT score (receiver operating characteristic area under the curve = 0.85). The probability of having AERD based on sinus CT score may be calculated using the equation $\exp[-2.496 + 0.1908 (\text{CT score})]/1 + \exp[-2.496 + 0.1908 (\text{CT score})]$ or by using the logistic regression curve (Fig 2). NP represents a complication of severe chronic sinusitis. Consistent with that concept, CT scores were much higher in patients with polyps (19.0 ± 5.9) than in those without polyps (6.1 ± 5.5 ; $P < .001$). Only 2 of 40 patients with a CT score higher than 12 did not have nasal polyps (both of these patients were aspirin intolerant). Reflecting the severity of their sinusitis hyperplasia, patients with AERD were much more likely to have NP (19/21) than those with aspirin tolerance (5/19; $P < .001$).

Inflammatory Markers

AERD was associated with a trend toward increased circulating absolute eosinophil counts (Table 3). However, no differences between total exhaled NO or exhaled breath condensate pH were observed.

DISCUSSION

The current study was performed to determine if AERD can be distinguished from ATA by the severity of the patients' CHES and, as such, whether the sinus CT scan can be used to predict the presence of aspirin intolerance. The extent of sinus disease was scored according to our previously published and validated methods.^{15,22,23} In these earlier studies, a sinus CT score of 12 or higher was interpreted as extensive sinus disease, based on the findings of correlations between this score and a history of asthma, elevated serum IgE levels, and eosinophilia.¹⁵ CT scores of 12 or higher were present in 5 (26%) of 19 control patients and 17 (81%) of 21 AERD patients (Fig 1), and, when calculated as a geometric mean, CT scores in AERD patients were significantly higher than those in patients with aspirin tolerance (16.9 vs 6.2; $P < .001$; Table 3). Although some overlap was evident, the probability of AERD may be predicted based on sinus CT score (Fig 2). The actual extent of these differences may have been mitigated, because many of the AERD patients had received therapeutic interventions, including surgery. However, we only scored CT scans obtained before medical interventions thought to be effective in CHES, such as aspirin desensitization^{24–26} or the 5-lipoxygenase inhibitor zileuton.²⁷ The extent to which interventions such as intranasal corticosteroids may have attenuated CHES severity is difficult to evaluate, however, insofar as the influence of these treatments on CT score has never been evaluated. We recognize that these data may exaggerate the severity of sinusitis in AERD, because our recruitment criteria reflected only patients with respiratory disease severe enough to warrant referral to specialty care; however, these data accurately reflect patients seen in asthma and allergy clinics.

Previous studies have estimated that approximately 74% to 90% of patients with asthma demonstrate some degree of pansinusitis.^{15–18} It has previously been stated that although this combination of pansinusitis and asthma should make the physician suspicious regarding the presence of aspirin intolerance, most patients with this presentation will never react to aspirin.²⁸ However, in studies that used our sinus CT scoring

Table 1. Baseline Demographics and Patient Characteristics

Variable	ATA patients (n = 19)	AERD patients (n = 21)
Age, geometric mean (IQR), y	46.0 (32.0–50.0)	47.0 (40.0–50.0)
Female, No. (%)	15 (79)	11 (52)
African American, No. (%)	2 (11)	4 (19)
Hispanic, No. (%)	1 (5)	0 (0)
Asthma duration, geometric mean (IQR), y*	17.5 (6.5–32.0)	9.5 (3.2–17.0)
Allergic rhinitis, No. (%)†	11 (58)	10 (48)
High-dose corticosteroids, No. (%)†	11 (58)	12 (57)
Leukotriene modifiers, No. (%)†	9 (47)	14 (67)
>2 rescue inhalations per week, No. (%)†	10 (53)	13 (62)

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; IQR, interquartile range.

* Between-group comparison ($P = .21$).

† Percentage of patients for whom information was available.

Table 2. Pulmonary Function Test Results*

Test	ATA patients (n = 19)	AERD patients (n = 21)	P value
FEV ₁ prebronchodilator*	83.0 (70.5–7.7)	84.7 (76.4–101.8)	.83
FEV ₁ postbronchodilator*	90.7 (79.3–103.7)	94.3 (86.3–103.0)	.63
Percent change	9.3 (4.4–14.4)	11.3 (6.8–16.0)	.16
FVC prebronchodilator*	89.4 (80.8–98.9)	96.8 (92.1–101.8)	.16
FVC postbronchodilator*	94.6 (88.3–101.6)	101.8 (96.3–107.6)	.10
Residual volume	106.0 (90.3–124.6)	114.7 (91.8–143.30)	.57
Total lung capacity	98.0 (93.7–102.5)	107.9 (99.9–117.6)	.05
DLco/AV	113.7 (105.6–122.4)	109.7 (102.1–117.8)	.48

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; DLco/AV, diffusing capacity corrected for alveolar volume; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

* Data are presented as geometric mean (95% confidence interval) of the percentage predicted.

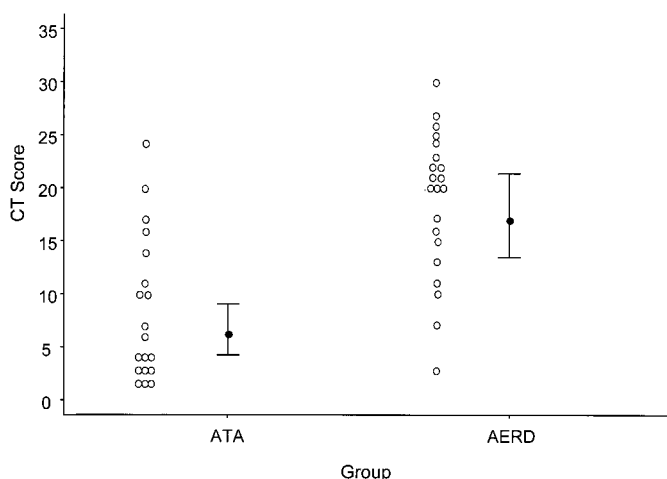


Figure 1. Chronic hyperplastic eosinophilic sinusitis severity by computed tomography (CT) score in patients with aspirin-tolerant asthma (ATA) compared with patients with aspirin-exacerbated respiratory disease (AERD). Individual data points (open circles) and geometric means (closed circles) with 95% confidence intervals (error bars) are shown.

system, and as confirmed in the current studies, CT scores higher than 12 are unusual in asthmatic patients who are not aspirin intolerant.^{15,17–19}

Nasal polyps were documented in 24 of 41 total patients in this study and 19 of 21 patients with AERD (Table 3). Thus, having nasal polyps had a predictive value similar to having a CT score greater than approximately 20 in predicting the presence of aspirin intolerance. An association of NP with severe CHES is not a surprising finding, since the original definition of triad asthma included the presence of nasal polyps. A correlation between the presence of NP and extensive CHES is similarly expected, because nasal polyps are thought to reflect in part a herniation of excessive hyperplastic tissue from the maxillary and anterior ethmoid sinuses into the nasal cavity. The strong association of NP with CT scores supports this concept. In fact, the 2 AERD patients without NP were the 2 patients shown in Figure 1 with the lowest CT scores. Interestingly, 1 of these 2 patients subsequently underwent a grade aspirin challenge and was found

not to have AERD. We include her data in the AERD cohort, because this article is designed to be a guideline for physicians who deal with the diagnosis of aspirin sensitivity in patients in whom only historical information is available. The absence of significant CHES on this patient's CT scan supports the validity of this diagnostic approach.

Medical history–based studies of aspirin intolerance may underestimate the extent of this disease because of patients either who do not require or who assiduously avoid use of COX inhibitors. For this study, all patients were required to have recently ingested a pharmacologically relevant concentration of a nonspecific COX inhibitor. Our diagnosis of aspirin intolerance was based on the patients' subjective feeling that exposure to aspirin was associated with cough, wheeze, or other symptoms of asthma. It was also verified in most cases during aspirin desensitization. Aspirin intolerance is properly diagnosed by performing a graded aspirin challenge or experimentally by topical challenges with lysine aspirin.^{3,5,6} This requires hospitalization and close observation and places the patient at risk of respiratory failure. Because of the inherent variability of lung function in asthma, temporal worsening of asthma in association with aspirin ingestion can be confused with evidence for hypersensitivity. Aspirin challenge fails to confirm AERD in approximately 15% of cases with a positive clinical history.^{3,5,6} Although we are confident that all of our patients who reported aspirin tolerance had ingested COX inhibitors without sequelae, we cannot be certain that all of the patients included in the AERD cohort would meet the criteria using an appropriately administered challenge technique.

Support for the theory that AERD represents a unique asthma syndrome is suggested by the much shorter duration of asthma observed in this cohort (Table 1) and the related observation that AERD is a disease of adult onset.³ It is intriguing to speculate that the increased severity and prevalence of remodeling reported in adult-onset asthma^{29,30} may reflect, in part, the prevalence of individuals with aspirin intolerance within this patient population.

It is frequently imperative to make the diagnosis of aspirin intolerance in asthmatic patients. Aspirin and other NSAIDs are seldom used in children. Later in life, once patients

Table 3. Inflammatory Markers

Marker	ATA patients (n = 19)	AERD patients (n = 21)	P value
CT score, geometric mean (95% CI)	6.2 (4.2–9.1)	16.9 (13.4–21.3)	<.001
Nasal polyps, No. (%)	5 (26)	19 (90)	<.001
Eosinophils, geometric mean (95% CI), / μ L	318 (243–417)	431 (313–593)	.15
Total IgE, geometric mean (95% CI), IU/mL	150.4 (75.2–300.7)	77.3 (41.4–144.5)	.16
Nitric oxide exhaled, geometric mean (95% CI), ppb	24.7 (16.5–36.9)	27.4 (17.0–44.0)	.74
pH, geometric mean (95% CI)*	7.88 (7.27–8.53)	7.50 (6.94–8.11)	.38

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; CI, confidence interval; CT, computed tomography.

* Exhaled breath condensate.

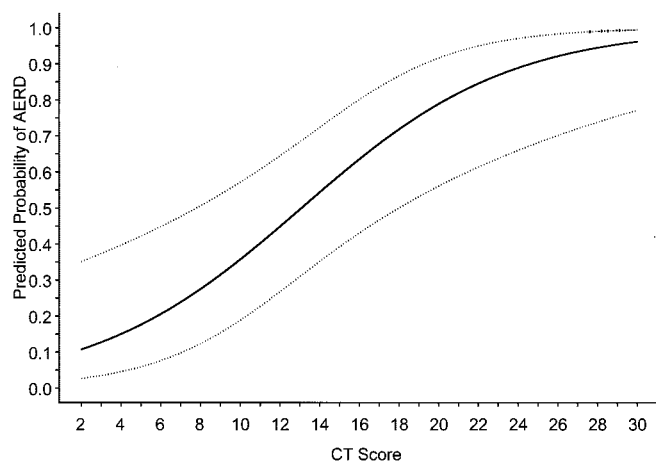


Figure 2. Predicted probability of aspirin-exacerbated respiratory disease (AERD) as a reflection of computed tomography (CT) score. The solid line represents the predicted probability of AERD, and the hatch lines represent the lower and the upper limits of the point-wise 95% confidence interval for the value of the predicted probability.

develop their asthma, these agents are frequently avoided because of the concerns regarding concomitant aspirin intolerance. It is therefore not unusual to identify patients with asthma who have never used aspirin or other NSAIDs. In these individuals, their safety cannot be determined when a need for their use develops, such as prophylaxis for coronary artery or cerebral vascular disease or as treatment for inflammatory disorders. In addition, understanding a patient's aspirin tolerance status can be used to predict responsiveness to therapeutic intervention with aspirin desensitization.^{24–26} Along with other clinical criteria (childhood onset of the asthma, presence of atopy, absence of nasal polyps, and absence of high-grade eosinophilia), our data suggest that the absence of significant sinus disease (CT score <12) would support the likelihood of aspirin tolerance in an individual either who had not ingested aspirin or NSAIDs or in whom the history of reactivity was ambiguous.

Studies of a compromise of lung function and remodeling in adult-onset asthma,^{29,30} AERD (unpublished observations), and patients with more severe sinusitis¹⁸ led us to predict that the AERD patients in our study would display diminished lung function. However, in contrast to these studies, our

control patients were recruited based on careful matching for asthma severity. The similarity in spirometry therefore reflects these recruitment criteria. However, our patients demonstrated increased total lung capacity, possibly reflecting a trend toward increased air trapping. This reported combination of increased airway remodeling in the lower airways concomitant with extensive hyperplastic sinus disease and nasal polyp formation supports the concept that these are similar pathologic processes that influence the lower and upper airways, respectively.

In summary, we compared the severity of sinus disease in patients with moderate-to-severe asthma with and without aspirin intolerance. Significant sinus disease and the presence of nasal polyps were strongly predictive of the presence of aspirin intolerance.

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