Published in final edited form as:

Ann Allergy Asthma Immunol. 2003 March ; 90(3): 316–322.

Sinus computed tomography scan and markers of inflammation in vocal cord dysfunction and asthma

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Abstract

Background: The inappropriate closure of the vocal cords is characteristic of vocal cord dysfunction (VCD). These patients present with wheezing and frequently receive a misdiagnosis of asthma.

Objective: To demonstrate the ability of computed tomography (CT) scored for the presence and extent of sinus disease and markers of inflammation to distinguish patients with VCD from patients with asthma.

Methods: Comparisons of 13 patients with VCD were made to 77 patients presenting to the emergency room with acute asthma, 31 non-acute asthmatic patients, and 65 nonasthmatic controls. Evaluation consisted of exhaled nitric oxide gas (eNO), circulating eosinophils, and total serum immunoglobulin (Ig)E, as well as the sinus CT scan.

Results: Extensive sinus CT changes were present in 23 of 74 acute asthmatic patients, 5 of 29 non-acute asthmatic patients, and 2 of 59 nonasthmatic controls. In addition, absolute eosinophil counts, eNO, and total IgE were significantly elevated among the asthmatic patients. Sinus symptoms reported by questionnaire did not predict sinus CT findings. Among the patients with VCD, none had extensive sinus disease. They also had normal eNO, low IgE, and normal eosinophil count. Five of the patients presenting to the emergency room who were identified as acute asthmatic were identified with VCD by laryngoscopy and were all characterized by the absence of significant inflammation on their sinus CT scan, low IgE, and normal eosinophil count.

Conclusions: Among patients presenting with intermittent or reversible airway obstruction, patients with VCD can be distinguished from asthma by minimum or absence of inflammation in their sinuses as shown by CT scan. Clinical symptom scores are not predictive of presence or extent of sinus disease in most cases.

INTRODUCTION

Vocal cord dysfunction (VCD), also known as episodic laryngeal dysfunction, laryngeal dyskinesia, paradoxical vocal fold dysfunction, or paradoxical laryngospasm, is characterized by the inappropriate closure of the vocal cords that can occur predominantly on inspiration.^{1–5} This airway obstruction is associated with dyspnea, cough, choking sensation, and stridor. Other symptoms variably associated with VCD include hoarseness, difficulty speaking, and dysphagia. The presence of episodic airway obstruction with stridorous wheezing and dyspnea leads to these patients being misidentified with asthma and to their being treated with asthma medications, including oral corticosteroids.

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Supported by a NIH grants AI01793 and AI50989

In contrast to VCD, asthma is an inflammatory disease of the lower airway characterized by activation of Th2-like lymphocytes and eosinophilia, goblet cell hyperplasia, mucous hypersecretion, smooth muscle hyperplasia with bronchospasm, and airway hyperreactivity. The bronchodilator and anti-inflammatory therapies including leukotriene modifiers and corticosteroids, which are used in asthma, are generally ineffective in VCD. The combination of the misdiagnosis of asthma in VCD with this failure of asthma pharmacotherapy often leads to these patients being subjected to multiple high-dose controller therapies and the frequent utilization of systemic corticosteroids.³ This failure to manage VCD properly is associated with tremendous health care utilization, as these patients are subject to frequent urgent care visits and hospitalizations and are often intubated.³ The diagnostic and therapeutic challenges posed by the need to distinguish VCD from asthma are further confounded by the observation that some patients suffer from a combination of asthma and VCD.

The diagnosis of VCD is suggested by the presence of a consistent medical history including symptoms of laryngeal stridor, choking sensation, voice changes, difficulty speaking, absence of sputum, and a greater difficulty with inspiration. VCD is typically triggered by strong odors such as cigarette smoke, perfume, and pollutants and, in contrast to asthma, typically improves with sleep.^{3,4} The diagnosis of VCD is supported by spirometry demonstrating fixed extrathoracic obstruction with truncation of the inspiratory loop.^{1,3,5} When VCD is suspected, the diagnosis can be established by laryngoscopic examination.¹⁻³ If performed at a time when the patient is symptomatic, laryngoscopy demonstrates the typical paradoxical closure of the vocal cords with a minimal aperture produced by the characteristic posterior “chink.”

Despite their unique clinical presentations, pathophysiologic mechanisms, and response to treatments, distinguishing VCD from asthma remains a clinical problem. As noted, asthma is distinguished from VCD in part by the presence of a potent inflammatory mechanism. The current studies were therefore performed to evaluate the utility of surrogate inflammatory markers in distinguishing these conditions. Cohorts of patients presenting to the University of Virginia Hospital emergency room (ER) or asthma clinics with acute or stable asthma and VCD were enrolled. We evaluated the usefulness of total serum immunoglobulin (Ig)E, soluble interleukin (IL)-2 receptor (CD25), exhaled nitric oxide (eNO), and absolute circulating eosinophil counts in distinguishing asthma from VCD. A link between sinusitis and asthma has long been recognized, and when adult asthmatic patients are evaluated by computed tomography (CT) scans, approximately 74 to 90% have some degree of mucosal hyperplasia.⁶⁻⁸ We therefore evaluated the utility of quantification of the presence and severity of sinusitis on the CT scan as an aid to distinguishing VCD and asthma.

METHODS

ER Subjects

The human investigations committee at the University of Virginia approved the protocol and informed consent was obtained from all subjects before enrollment. The study population included 77 patients who presented to the ER between August and March and were identified with acute asthma. Entrance criteria required that patients were between the ages of 18 to 50 years, reported a history of asthma, and presented with the complaint of acute dyspnea. All subjects were questioned regarding symptoms and medical history of asthma and sinus disease as well as a detailed medication and smoking history. Asthmatic patients were asked about the duration of their disease and the frequency and number of exacerbations. Patients over the age of 50 were excluded to minimize the inclusion of subjects with chronic obstructive pulmonary disease. All subjects had wheezing on examination and standard therapy was administered in the ER at the discretion of the ER physicians. Subjects performed standard spirometry (flow-volume evaluation), exhaled breath was collected for eNO analysis, and blood was drawn for complete blood count, absolute eosinophil count, total IgE, serum eosinophil cationic protein

(ECP), soluble IL-2 receptor, and serum IL-13. Nasal secretions were obtained by lavage with 7 to 9 cc of normal saline for detection of rhinovirus using the reverse-transcriptase polymerase chain reaction analysis. Within 10 days, a coronal low-dose sinus CT ("screening" CT) was obtained to depict the anatomy of the nasal cavity and to evaluate the sinuses for mucosal inflammatory change. Six asthmatic subjects were not included in the final analysis. Four did not return for followup CT within 10 days. One subject was excluded from study after reporting being pregnant and a second subject was excluded after being identified with congestive heart failure after enrollment in the study.

Non-Acute Asthmatic Subjects

Thirty-one non-acute asthmatic subjects were recruited for these studies. These subjects had mild symptoms only at the time of enrollment and had not had an asthma exacerbation requiring oral corticosteroids, change in medication, or urgent care within 2 months. The diagnosis of asthma was established based on medical history, medication usage, and documentation of reversible obstructive lung disease ($\geq 12\%$ improvement of forced expiratory volume in 1 second after administration of a bronchodilator). This cohort included 5 subjects who were given the diagnosis of asthma who presented to the ER but were stable at the time of presentation with complaints unrelated to their asthma and 26 subjects recruited from the asthma and allergy/immunology clinics at the University of Virginia.

Control Nonasthmatic Subjects

A control population was recruited from the ER. They were enrolled concurrently with the asthmatic subjects and were matched for age, sex, and race. Controls were excluded from enrollment if they complained of shortness of breath or carried the diagnosis of asthma ($n = 5$). The final study population included 65 control subjects. Eight control subjects did not return for a sinus CT scan and were excluded from analysis.

VCD Subjects

Subjects who presented to the ER with acute airway obstruction in whom the diagnosis of VCD was suspected underwent diagnostic laryngoscopy. The diagnosis of VCD was suggested by a combination of relevant medical history or pulmonary spirometry that demonstrated truncation of the inspiratory loop. Laryngoscopy was performed on 12 of the 77 subjects and VCD confirmed in 5 on the basis of the presence of inappropriate approximation of the vocal cords with a posterior chink. An additional 13 patients were recruited from the allergy/immunology and asthma clinics of the University of Virginia; they had previously been diagnosed with VCD confirmed on the basis of consistent findings observed on laryngoscopy. Although VCD is known to occur in the concomitant presence of asthma, these subjects were not thought to have asthma.

Sinusitis History

A modification of a symptom-based survey of chronic sinusitis was used to gauge the severity of sinus symptoms in all subjects presenting to the ER.⁹ This questionnaire included reported symptoms of facial pain or pressure, posterior pharyngeal drainage, nasal congestion, rhinorrhea, and antibiotic use. Forty-two percent (32 of 76) of the acute asthmatic patients and 34% (18 of 53) of the control subjects reported symptoms considered to be consistent with sinus disease, which was also reported in 90% of the non-acute asthmatic patients and 77% of the VCD subjects (Table 1).

eNO

eNO was collected in all subjects by having the subjects slowly exhale into a NO-impermeable Mylar balloon (Amscan, Harrison, NY).^{10,11} The mouthpiece was narrow enough (5-mm

diameter) to create positive back pressure, sufficient to close the vellum and thus isolate the eNO from contamination by the nasal passages and sinus cavities.^{11,12} Exhaled gas samples were analyzed for eNO within 1 hour of collection using the Sievers NOA 240 chemiluminescence analyzer (Sievers Instruments, Boulder, CO).

Computerized Tomography

Subjects underwent a coronal helical CT scan in a prone position after clearing the nose and administration of a nasal decongestant. The scans were of 1.5-mm thickness and acquired at 3-mm intervals. Thirty-nine of 71 acute asthmatic patients were scanned within 72 hours (range 0 to 9 days) and non-acute asthmatic, VCD, and control subjects were scheduled electively. All CT scans were assigned a quantitative score by one investigator (C.D.P) who was blinded to the clinical condition. The extent of sinus disease was scored according to previously published methods.^{6,13,14} A sinus CT score of ≥ 12 was interpreted as extensive sinus disease based on the previous findings of correlations between this score and a history of asthma, elevated serum IgE levels, and eosinophilia.⁶

Inflammatory Markers

As reported previously, blood samples were analyzed for a complete blood count that included a total eosinophil count by an automated system. Serum was separated after 1 hour at room temperature and stored at -35°C . Serum was processed for total serum IgE and ECP using the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). Soluble IL-2R and IL-13 were assayed in serum via commercial enzyme-linked immunoadsorbent assay (R&D Diagnostics, Minneapolis, MN).

Statistical Analyses

Comparisons were performed between 77 ER patients with acute asthma, 31 non-acute asthmatic patients, 65 nonasthmatic controls, and 13 VCD patients. For the purposes of these analyses, subjects presenting to the ER who were subsequently identified with VCD are analyzed in the ER cohort. The results for CT scans were not normally distributed; thus, all data were analyzed using nonparametric tests.¹⁵ Comparisons of nominal data between groups were performed using the Mann-Whitney test. χ^2 analysis was used to compare dichotomous data, and the Fisher's exact test was performed if the sample size was <10 . Analysis of multiple groups was performed with the Kruskal-Wallis analysis of variance ranks test and a Newman-Keuls posthoc test for significance. Correlations were performed using the Spearman rank sum method and P value of <0.05 was considered significant. All data are expressed as the mean $\pm$ standard error of the mean.

RESULTS

Population Demographics

The control and asthmatic ER subjects and non-acute asthmatic subjects were well matched in terms of sex and racial characteristics (Table 1). Mean age of the asthma group was slightly older than the control subjects, 32.8 ± 1.0 years versus 30.4 ± 1.1 , respectively. VCD subjects were older (46.8 ± 2.5 years) and were all female. A history of smoking was present in 43.7% of the acute asthmatic patients, 29% of the non-acute asthmatic patients, and 50.0% of the controls but not in any of the VCD subjects.

Sinus CT Findings

Extensive sinus disease (CT score ≥ 12) was present in 23 of 74 (31.1%) of the acute asthma subjects, 5 of 29 (17.2%) of the non-acute asthmatic patients, and in only 2 of 57 (3.5%) nonasthmatic controls (Table 2, Fig 1). None of the VCD subjects had CT scores ≥ 12 ($P <$

0.0001). Lesser degrees of CT abnormalities (CT score 3 to 11) were common in all four cohorts: 35 of 74 (47.3%) acute asthmatic patients; 15 of 29 (51.7%) non-acute asthmatic patients; 29 of 57 (50.9%) controls; and 2 of 13 (15.4%) VCD; $P = \text{n.s.}$). More CT scans in the control group (26 of 57; 45.6%) scored between 0 to 2, but 16 of 74 (21.6%) of the patients with acute airway obstruction also had low scores as did 9 of 29 (31.0%) of the non-acute asthmatic subjects. Sinus disease (CT score ≥ 3) was present in only 4 of 13 (30.8%) of the VCD subjects and the highest observed CT score was 5 ($P < 0.0001$ compared with acute and non-acute asthma). Of the patients presenting to the ER with acute airway obstruction, VCD was subsequently diagnosed by history, spirometry, and subsequent laryngoscopy in 5 of them. CT scans were performed in four of these subjects and were < 3 in 2 of 4. Three acute asthma patients had CT scores of ≥ 23 , and each of these had a history of respiratory failure related to the ingestion of aspirin or a nonsteroidal anti-inflammatory agent (two during the episode studied here and one previously by history). All three of the non-acute asthmatic subjects with CT scores ≥ 23 had aspirin-intolerant asthma.

There was no correlation between the presence or extent of sinus disease as determined by CT scan and either the clinical diagnosis of acute bacterial sinusitis or administration of an antibiotic by the ER physician. Similarly there was no correlation between CT scan results and the presence of sinusitis symptoms as reported on the questionnaire ($r^2 = 0.18$).

Eosinophil Count and Total IgE

As a group, the asthmatic patients had threefold higher absolute eosinophil counts (389 ± 50 cells/ μL) compared with controls (Table 2; 99 ± 7 cells/ μL ; $P < 0.0001$). Non-acute asthmatic patients had intermediate values (290 ± 52). Subjects with VCD had absolute eosinophil counts not significantly different from those of control subjects (118 ± 18). For the five subjects who presented to the ER with complaints of acute airway obstruction and were subsequently identified as having VCD, their absolute eosinophil count was later shown to be 59 ± 16 (range 5 to 86). Mean serum IgE levels were substantially greater in the asthmatic group (385 ± 58 IU/mL) than in controls (152 ± 37) and, as with the absolute eosinophil count, non-acute asthmatic patients had an intermediate value (286 ± 75 ; $P < 0.0001$). Subjects with VCD had total serum IgE concentrations indistinguishable from nonasthmatic subjects (46 ± 14). Among the acute patients shown to have VCD, their total IgE concentrations were subsequently found to be normal (56 ± 25 ; range 6 to 146). Taking the whole group, there was a significant univariate association between total IgE and sinus CT score ($n = 131$, $r = 0.31$, $P < 0.001$). This relationship was still significant when the cohort of asthmatic subjects was analyzed ($n = 70$, $r = 0.27$, $P = 0.02$). However, the striking feature was that the 33 asthma patients with extensive sinus disease had a mean total IgE of 500 ± 104 IU/mL. There was not a significant association between absolute eosinophil count and sinus CT score, although subjects with CT scores ≥ 12 tended to have higher eosinophil counts (365 ± 63) than those with CT scores < 12 (237 ± 28 ; $P = 0.06$).

Markers of Inflammation

Mean eNO was 15.8 ± 0.9 parts per billion among the acute asthma group, 13.5 ± 1.5 for the non-acute asthma group, and 9.7 ± 1.0 parts per billion for the control group, ($P < 0.001$).⁹ Similar to eosinophilia and sinus CT scores, the eNO concentrations among VCD patients were not significantly different from control subjects (8.0 ± 3.5), including the ER subjects subsequently identified as having VCD (10.4 ± 0.8). The results for eNO were not significantly related to the CT findings in the patients with asthma. Serum ECP was 33.2 ± 4.1 U/mL in the asthma patients compared with 15.1 ± 1.1 in the control subjects ($P < 0.001$), which is consistent with eosinophil activation. Serum ECP was not included in further analyses because preliminary analysis showed colinearity with absolute eosinophil count ($r = 0.43$, $P < 0.001$). Although the total WBC counts were higher in the asthma subjects than in the controls, the

absolute numbers of lymphocytes and neutrophils were similar for the asthma patients ($2,050 \pm 118$ cells/ μ L and $5,303 \pm 306$ cells/ μ L) and for the control subjects ($1,881 \pm 72$ cells/ μ L and $4,633 \pm 303$ cells/ μ L, respectively). Neither circulating serum IL-2 nor serum IL-13 concentrations distinguished control subjects from those with acute asthma (Table 2), and these analyses were therefore not performed on the VCD cohort.

DISCUSSION

These studies support the concept that events in the upper airway that cause airway obstruction in VCD are not related to generalized airway inflammation. Among patients presenting with intermittent or reversible airway obstruction, patients with VCD can be distinguished from those with asthma by the minimum or absence of inflammation in their sinuses as shown by CT scan and by the absence of elevated eNO, peripheral blood eosinophilia, and normal circulating total IgE concentrations. Our results confirm the presence of a highly significant association between sinus abnormalities seen on CT and asthma.^{6–8} However, the results also make it clear that it is essential to use a scoring system and to compare CT results to a “normal range,” as minor abnormalities are present in a large proportion of the controls. Using our definition of extensive disease (CT score ≥ 12), sinusitis was present in 23 of 74 (31.1%) acute asthmatic patients presenting to the ER but not in any of the VCD subjects. Further, in comparison to the study controls, fewer VCD subjects demonstrated minor abnormalities in their sinus disease. This may plausibly reflect the frequent use of systemic corticosteroids in these subjects who are frequently placed on these therapies after being misdiagnosed with asthma. Our results confirm a previous suggestion made by Newman et al,³ using standard anterior-posterior radiography of the sinuses, that VCD subjects demonstrate less evidence for sinus disease and diminished eosinophilia than those with asthma.

In the present study we found very little relationship between questionnaire results and sinus CT changes. These results confirm previous published evidence that clinical symptom scores are not predictive of either the presence or extent of sinus disease in most cases.^{6–8,16} This is not surprising insofar as many of the symptoms that are used to evaluate sinus disease such as headache, posterior pharyngeal drainage, purulent nasal drainage, nasal congestion, and toothache are not specific for this disease. These symptoms are more reflective of the presence of nasal disease including all of the causes of perennial rhinitis. Similarly, frontal headaches have numerous causes and the source of this discomfort can not be localized by the patient with any accuracy to the sinuses. In the current study, neither fever nor neutrophil leukocytosis was associated with the presence or extent of sinus disease. We assume that most of the sinus opacification represents some form of inflammation including goblet cell hyperplasia and mucus hypersecretion, but also cellular infiltration of the tissues with eosinophils, lymphocytes, monocytes, basophils, and mast cells.^{17–19} This opacification will also reflect the fibroblast hyperplasia, collagen deposition, and fibrosis associated with this chronic inflammatory process. However, it is likely that chronic sinusitis represents numerous disease processes including those with more prominent eosinophilic inflammation and those more characterized by either mononuclear inflammatory cells or alternatively mucous hyperplasia without prominent active inflammation. This inflammation in many or perhaps most cases does not seem to be related to the presence of a bacterial infection.^{20,21}

Similar to the questionnaire results, in our retrospective analysis, no association was observed between the decision of the ER physician to discharge two of the patients on an antibiotic for acute sinusitis with findings suggestive of acute sinusitis on their CT scan. Unfortunately, other than the screening CT scan, no readily accessible methodology exists to assist in the diagnosis of acute bacterial sinusitis.

In our study, three individuals who presented to the ER with acute asthma and also three of the subjects recruited from the clinic with non-acute asthma had late-onset, severe asthma associated with intolerance to aspirin or other non-steroidal anti-inflammatory drugs. As has been previously published,¹⁴ each of these six cases had very extensive CT changes (CT score ≥ 23). In contrast, the majority of the patients with extensive sinus abnormalities (score ≥ 12) had the features of extrinsic asthma and the mean total IgE in this group was strikingly elevated. The association between elevated IgE and extent of sinus disease has been reported in chronic sinusitis, but not previously in relation to asthma.^{6,22}

Our results do not define how much of the changes seen were related to the acute episode. We have previously published that repeat CT on 13 of these cases after 4 to 6 months found a significant decrease in score but the changes were very variable.¹⁴ Similarly, the generally lower CT scores observed in our non-acute asthmatic patients suggests that some of the severity of the sinus disease observed in the ER cohort may have been related to the acute process responsible for the asthma exacerbation. It is tempting to propose that acute viral infection among patient would precipitate increased sinus changes and an exacerbation of asthma.^{23–25} Further understanding of the relationship between sinus disease and exacerbations of asthma will need prospective studies in which the change in sinus CT at the time of an attack can be related to evidence of viral infection, allergen exposure, and inflammation. However, the problem will remain difficult to resolve without better understanding of the immunologic mechanisms that lead to persistent eosinophil-rich inflammation in the sinuses.^{17–19}

Other evidence related to inflammation in the lower and upper airways can be obtained from eNO, nasal or blood eosinophils, and most recently, from condensates of exhaled air.^{10,26–28} Although we were unable to confirm a linkage of asthma to elevated circulating soluble IL-2 receptor or to IL-13, these studies did confirm a significant elevation of eNO and blood eosinophils (or the associated eosinophil marker, ECP) in asthma. Although sinusitis is associated with dramatically elevated NO production, our technique for measuring eNO should have been able to exclude NO derived from the sinuses.¹² Consistent with the sinus CT results, airway obstruction in VCD is not related to generalized airway inflammation. As such, in addition to the absence of significant sinusitis, VCD is not associated with elevations either in IgE, eosinophil counts, or eNO, and these parameters were identical to those observed in nonallergic subjects (Table 2).

A final, very important outcome of this study is the observation that VCD is not a rare condition and is a frequent presentation in the non-referral ER population. Patients were identified in the ER as having probable VCD on the basis of history and a flow-volume loop demonstrating inconsistency and evidence for fixed extrathoracic obstruction. Twelve of these patients underwent laryngoscopy, and the diagnosis of VCD was confirmed in five. Although it is well recognized that some patients with VCD also have asthma and sinus disease, many have vocal cord abnormalities *without* asthma.^{1,3,5,29} In the present study, these VCD subjects were subsequently shown to have low total IgE, absolute eosinophil counts $\leq 100/\mu\text{L}$, and, in the four subjects who subsequently had CT scans, scores of 0, 1, 4, and 5 (ie, they had no evidence for an inflammatory process). Thus, the investigations used here could provide a basis for identifying VCD and distinguishing VCD from asthma. A large portion of patients with VCD are inappropriately treated with oral steroids.³ Given that over a million patients are treated for asthma in the ER annually, and that this is a major, if not the only, way in which socio-economically disadvantaged patients present, investigation of these patients should be normal practice. Identifying these cases of VCD in the ER presents a challenge. However, investigations similar to those reported here can provide the information necessary to identify those patients who should be considered for specific treatments of VCD including speech therapy, heliox, and psychologic counseling. Although screening CT scans may be expensive to perform (approximately 600 to \$800), and this expense will generate reticence among third-

party payers to their approval, clearly this expense is much less than the cost of the misdiagnosis of asthma.

CONCLUSION

Our studies demonstrate the association of asthma with sinus abnormalities in approximately one-third of patients presenting to the ER with asthma. There was very little relationship between sinus symptoms and the presence or extent of disease on sinus CT. In contrast, VCD was not associated with sinusitis. Similarly, elevated IgE, eNO, and peripheral blood eosinophilia were associated with the presence of asthma but not with VCD. Among patients presenting with intermittent or reversible airway obstruction, patients with VCD can be distinguished from asthma by the minimum or absence of inflammation in their sinuses as shown by CT scan and by the absence of elevated eNO, peripheral blood eosinophilia, and normal circulating total IgE concentrations. VCD is a surprisingly common condition and must be considered in the evaluation of subjects with severe or difficult-to-control, intermittent obstructive airway disease.

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Figure 1. Sinus CT in obstructive lung disease.

The study population included healthy control subjects, patients who presented to the ER with the diagnosis of acute asthma, non-acute asthmatic subjects, and subjects with documented VCD. Subjects underwent a coronal helical CT scan which was assigned a quantitative score by one investigator (C.D.P.) using the previously validated methodology.

Table 1

Demographics of the Study Subjects

	Control	Acute asthma	Non-acute asthma	VCD
N	65	77	31	13
Age (range)	30.4 ± 1.1 (18–48)	32.8 ± 1.0 (18–50)	34.4 ± 1.9 (19–54)	46.8 ± 2.5 (27–57)
African-American (%)	30/62 (48.4%)	31/71 (43.7%)	8/3 (25.8%)	2/13 (15.4%)
Sex (F:M)	50:15	56:21	21:10	13:0
Smokers	31/62 (50.0%)	31/71 (43.7%)	9/31 (29.0%)	0 (0%)
Sinus symptoms (%)	18/53 (34.0%)	32/76 (42.1%)	27/30 (90.0%)	10/13 (76.9%)

VCD, vocal cord dysfunction.

Table 2**Markers of Inflammation**

	Controls	Acute asthmatic patients	Non-acute asthmatic patients	VCD
Sinus CT score (mean $\pm$ SEM)	4.1 $\pm$ 0.5 (57)	8.5 $\pm$ 0.8 (74)	7.3 $\pm$ 1.6 (29)	1.7 $\pm$ 0.5 ^{*†} (13)
Extensive sinus disease (CT score $\geq$ 12)	2/57 (3.5%)	23/74 (31.1%)	5/29 (17.2%)	0/13 (0%) ^{*†}
Normal sinus CT (score <3)	26/57 (45.6%)	16/74 (21.6%)	9/29 (31.0%)	9/13 (69.2%) ^{*†}
Absolute eosinophil count (cells/ μ L)	99 $\pm$ 7	389 $\pm$ 50	290 $\pm$ 52	118 $\pm$ 18 ^{*†}
ECP (U/mL)	15.1 $\pm$ 1.1	33.2 $\pm$ 4.1 [‡]	n.d.	n.d.
Total IgE (IU/mL)	152 $\pm$ 37	385 $\pm$ 58	286 $\pm$ 75	46 $\pm$ 14 ^{*†}
eNO (ppb)	9.7 $\pm$ 1.0	15.8 $\pm$ 0.9	13.5 $\pm$ 1.5	8.0 $\pm$ 3.5 ^{*†}
sIL-2R (U/mL)	660 $\pm$ 65 (59)	627 $\pm$ 40 (66) [†]	n.d.	n.d.
IL-13 (pg/mL)	5.0 $\pm$ 0.9 (51)	3.4 $\pm$ 0.2 (68) [†]	n.d.	n.d.

Values are mean $\pm$ SEM and (numbers of subjects tested).

Analysis of multiple groups was performed with the Kruskal-Wallis analysis of variance ranks test and a Newman-Keuls posthoc test for significance.

* $P < 0.0001$ compared to acute and non-acute asthmatics;

[†] $P =$ n.s. compared to controls,

[‡] $P < 0.001$ compared to controls.

Serum ECP was not included in the analysis of VCD patients as preliminary analysis showed colinearity with eosinophil count. sIL-2R and IL-13 analyses were not performed on the VCD subjects as these parameters did not distinguish control from acute asthmatic subjects.

VCD, vocal cord dysfunction; CT, computed tomography; ECP, eosinophil cationic protein; IgE, immunoglobulin E; eNO, exhaled nitric oxide; sIL-2R, soluble interleukin-2 receptor; IL, interleukin; SEM, standard error of mean; n.d., not done.