Original Article

Sinus Surgery Is Associated with a Decrease in Aspirin-Induced Reaction Severity in Patients with Aspirin Exacerbated Respiratory Disease

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> *What is already known about this topic?* Nasal polyps influence the burden of aspirin-exacerbated respiratory disease (AERD) by contributing to eicosanoid production.
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> *What does this article add to our knowledge?* In patients with AERD, sinus surgery lessens aspirin reactivity during graded challenges. The loss of aspirin sensitivity is associated with characteristic changes in urine and plasma eicosanoid levels and in circulating eosinophils.
>
> *How does this study impact current management guidelines?* Aspirin challenges after endoscopic sinus surgery (ESS) are more likely to be asymptomatic. Diagnostic aspirin challenges should be offered to patients with suspected AERD before ESS to increase diagnostic accuracy. Patients with established AERD should undergo aspirin desensitizations after ESS.

BACKGROUND: Nasal polyps influence the burden of aspirin-exacerbated respiratory disease (AERD) by contributing to eicosanoid production. AERD is diagnosed through graded aspirin challenges. It is not known how sinus surgery affects aspirin challenge outcomes.

OBJECTIVE: To investigate the effects of endoscopic sinus surgery (ESS) on aspirin-induced reaction severity and on the levels of eicosanoids associated with these reactions.

METHODS: Twenty-eight patients with AERD were challenged with aspirin before and 3 to 4 weeks after ESS. Respiratory parameters and plasma and urine levels of eicosanoids were compared before and after challenges.

RESULTS: Before ESS, AERD diagnosis was confirmed in all study patients by aspirin challenges that resulted in hypersensitivity reactions. After ESS, reactions to aspirin were less severe in all patients and 12 of 28 patients (43%, $P < .001$) had no detectable reaction. A lack of clinical reaction to aspirin was associated with lower peripheral blood eosinophilia (0.1 K/µL [interquartile range

(IQR) 0.1-0.3] vs 0.4 K/µL [IQR 0.2-0.8]; $P = .006$), lower urinary leukotriene E_4 levels after aspirin challenge (98 pg/mg creatinine [IQR 61-239] vs 459 pg/mg creatinine [IQR 141-1344]; $P = .02$), and lower plasma prostaglandin D_2 to prostaglandin E_2 ratio (0 [±0] vs 0.43 [±0.2]; $P = .03$), compared with those who reacted.

CONCLUSIONS: Sinus surgery results in decreased aspirin sensitivity and a decrease in several plasma and urine eicosanoid levels in patients with AERD. Diagnostic aspirin challenges should be offered to patients with suspected AERD before ESS to increase diagnostic accuracy. Patients with established AERD could undergo aspirin desensitizations after ESS as the severity of their aspirin-induced hypersensitivity reactions lessens. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1580-8)

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Abbreviations used
AERD- Aspirin-exacerbated respiratory disease
COX- Cyclooxygenase
ESS- Endoscopic sinus surgery
FeNO- Fractional exhaled nitric oxide
FEV1- Forced expiratory volume in 1 second
HETE- Hydroxyeicosatetraenoic acid
IQR- Interquartile range
LTE$_4$- Leukotriene E$_4$
LO- Lipoxygenase
NPF- Nasal inspiratory peak flow
NSAID- Nonsteroidal anti-inflammatory drug
PGD$_2$- Prostaglandin D$_2$
PGDM- Prostaglandin D$_2$ metabolite
PGDS- PGD$_2$ synthase
PGE$_2$- Prostaglandin E$_2$

Aspirin-exacerbated respiratory disease (AERD) is a subset of asthma characterized by the triad of nasal polyposis, asthma, and respiratory reactions to cyclooxygenase 1 (COX-1)—inhibiting medications.[1] AERD is diagnosed by a graded aspirin challenge that results in characteristic upper and lower respiratory symptoms.[2,3] Though the understanding of the pathogenesis of AERD is limited,[4] changes in the respiratory tissue of patients with AERD are apparent. Nasal polyp fibroblasts of patients with AERD lack prostaglandin E$_2$ (PGE$_2$) synthase and subsequently produce low levels of PGE$_2$; there is also resistance to PGE$_2$ anti-inflammatory effects due to the lack of E-prostanoid 2 receptor expression.[5-7] The lack of PGE$_2$ and the reduction of its effects on the respiratory tissue is one of the important features of AERD. PGE$_2$ inhibits proinflammatory 5-lipoxygenase (5-LO) expression and production of leukotriene B$_4$, while activating the 15-LO pathway.[8] This leads to an in increase in 15-hydroxyeicosatetraenoic acid (15-HETE), which is the precursor of another anti-inflammatory eicosanoid—lipoxin A$_4$.[8,9] In patients with AERD, higher baseline 15-HETE levels were associated with symptom improvement during aspirin treatment.[10] Levels of lipoxin A$_4$ and 15-epi-lipoxin A$_4$ are significantly lower in patients with AERD compared with patients with aspirin-tolerant asthma.[11,12]

In nasal polyp tissue, low PGE$_2$ in conjunction with high prostaglandin D$_2$ (PGD$_2$) levels and the resulting high PGD$_2$/PGE$_2$ ratio are characteristic of AERD.[6,13-15] The levels of several eicosanoids change during acute hypersensitivity reaction to aspirin challenge: both leukotriene E$_4$ (LTE$_4$) and PGD$_2$ increase after the reaction locally and systemically.[16-18] High urinary prostaglandin D$_2$ metabolite (PGDM) levels are associated with a more severe bronchospasm during aspirin challenges.[13,19,20] Urinary LTE$_4$ levels are positively correlated with reaction severity during aspirin challenges.[21]

These observations suggest that the removal of the nasal polyps might alleviate AERD disease burden, at least temporarily. However, the effects of nasal polyp excision by endoscopic sinus surgery (ESS) on clinical reactions to aspirin and on eicosanoid levels during aspirin challenges have not been well described. Except for the decrease in urinary LTE$_4$ levels,[22] it is not known whether ESS leads to changes in eicosanoid levels in plasma or urine, and if so, whether such changes are associated with changes in severity of clinical reactions during aspirin challenges. In this study, we sought to examine the influence of

ESS on aspirin challenge clinical outcomes. We hypothesized that ESS would lead to attenuation of the aspirin-induced hypersensitivity reactions during aspirin challenges in patients with AERD and to a decrease in urinary LTE$_4$ and PGD$_2$, and an increase in plasma lipoxin A$_4$ levels.

METHODS
Patients
Patients aged 18 years or older with a diagnosis of AERD were recruited in the study. Inclusion criteria comprised documented history of asthma and nasal polyps, chronic rhinosinusitis, and at least 1 clinical adverse reaction to any COX-inhibitor, stable asthma (baseline forced expiratory volume in 1 second [FEV1] >70% of predicted and no asthma exacerbations for at least 2 months before the first challenge), stable asthma treatment for a minimum of 4 weeks, and oral montelukast 10 mg daily for at least 1 week before aspirin challenges. All patients had nasal polyps and were planning to have aspirin desensitization as part of their routine medical care. All patients signed an informed consent at the time of enrollment, which was approved by the Institutional Review Board at Albert Einstein College of Medicine.

Study protocol
This was a prospective observation trial. All patients underwent a diagnostic oral graded aspirin challenge to confirm aspirin sensitivity. For the graded challenge, 40 mg of aspirin (dissolved Original Alka-Seltzer) was initially administered and then the dose was doubled every 60 minutes (80, 160, and 325 mg).[23] The diagnosis of AERD was established by the presence of a positive aspirin challenge, defined as characteristic sinonasal symptoms and/or ≥15% decline in FEV1. Patients were treated on the basis of their specific symptoms after aspirin-induced hypersensitivity reactions. After confirming the diagnosis, patients were scheduled for ESS within 12 months from the time of the initial aspirin challenge. Three to four weeks after ESS, patients had another aspirin challenge and subsequent desensitization to aspirin. At least 1 week before each of the 2 challenges, all patients took 10 mg of montelukast daily.[20] No participants were taking zileuton before challenges. Patients were required to be off oral corticosteroids for at least 1 week before the challenges (unless on chronic oral prednisone).[24] All patients continued using their prescribed inhaled corticosteroids with or without long-acting β-agonists at the time of the study, and there was no change in their medications between the 2 challenges. Patients were observed for upper and lower respiratory symptoms, ocular injection, rash, and abdominal pain.

TABLE I. Patients' characteristics

Patients with AERD, N = 28	
Age (y), mean ± SE	46 ± 2.7
Female patients, N (%)	18 (67)
Race, N (%)	
African American	14 (50)
Latino	7 (25)
White	7 (25)
ICS/LABA use, N (%)	23 (82)
Oral corticosteroids use, N (%)	3 (11)

AERD, Aspirin-exacerbated respiratory disease; *ICS*, Inhaled corticosteroids; *LABA*, long-acting β-agonists; *SE*, standard error.

TABLE II. Characteristics of patients during the aspirin challenge before and after surgery

	Before surgery	After surgery	P value
Baseline FEV1, % predicted (±SEM)	83.7 ± 4.3	83.9 ± 4.3	.9
No. of patients with no clinical symptoms during aspirin challenge, N (%)	0	12 (43)	<.001
Decrease in FEV1, % predicted during hypersensitivity reaction to aspirin, % median (IQR)	−10.0 (−19.0 to −3.8)	−8.6 (−14.0 to −2.4)	.02
Minimal FEV1 % value during hypersensitivity reaction to aspirin, % (±SEM)	68.0 ± 3.9	78.0 ± 4.9	.04
Baseline nasal peak flow, L/min (±SEM)	107.0 ± 8.6	141.0 ± 9.0	.003
Decrease in nasal peak flow, % median (IQR)	−26 (−45 to −16)	−13 (−20 to 4)	.001
Minimal nasal peak flow during hypersensitivity reaction to aspirin (L/min), median (IQR)	80 (30-100)	130 (90-170)	<.001
FeNO (ppb), median (IQR)	45 (28-69)	28 (16-44)	.006
FeNO decrease during aspirin desensitization, % median (IQR)	−23 (−41 to −17)	−13 (−32 to −2)	.04
Time in minutes to the onset of the hypersensitivity reaction after provoking dose, mean (±SEM)	43 (±5.7)	38 (±5.0)	.5
No. of aspirin doses before hypersensitivity reaction onset, median (IQR)	2 (1-2)	2 (1-2)	.8
Aspirin provoking dose (mg), median (IQR)	80 (40-80)	80 (40-80)	.5
No. of aspirin doses before hypersensitivity reaction onset, median (IQR)	2 (1-2)	2 (1-2)	.8
Baseline peripheral blood eosinophil counts (K/μL), median (IQR)	0.7 (0.4-0.8)	0.3 (0.1-0.5)	.003

FeNO, Fractional exhaled nitric oxide; *FEV1*, forced expiratory volume in 1 s; *IQR*, interquartile range; *SEM*, standard error of the mean.

TABLE III. Characteristics of aspirin reactors post-ESS vs aspirin nonreactors

	No reaction, N = 12	Reacted to challenge, N = 16	P value
Age (y), mean ± SE	50.6 ± 4.4	42.5 ± 3.1	.1
Female patients, N (%)	9 (75)	9 (56)	.4
Race, N (%)			.99
African American	6 (50)	8 (50)	
Latino	3 (25)	4 (25)	
White	3 (25)	64 (25)	
Baseline FEV1, % predicted, median (IQR)	95 (76-109)	75 (64-95)	.1
Decrease in FEV1 % during hypersensitivity reaction to aspirin (%), median (IQR)	−5.3 (−7.3 to 0)	−10.7 (−18 to −3)	.04
Minimal FEV1 % value during hypersensitivity reaction to aspirin (%), median (IQR)	82 (71-100)	67 (54-88)	.08
Baseline nasal peak flow, L/min (±SEM)	125 ± 17	148 ± 9	.2
Decrease in nasal peak flow (%), median (IQR)	0 (−7.1 to 6.3)	−14.0 (−21.0 to −2.3)	.02
Minimal nasal peak flow during hypersensitivity reaction to aspirin (L/min), median (IQR)	120 (70-170)	130 (100-160)	.8
FeNO (ppb), median (IQR)	18 (15-34)	31 (27-51)	.06
FeNO decrease during aspirin challenge (%), median (IQR)	−4 (−21 to 18)	−16 (−33 to −7)	.07
Baseline peripheral blood eosinophil counts (K/μL), median (IQR)	0.1 (0.1-0.3)	0.4 (0.2-0.8)	.006
Last aspirin dose before the second post-ESS challenge, weeks (IQR)	15 (8-19)	12 (9-26)	.8
No. of surgeries before enrollment, median (IQR)	1 (0-1)	1 (0-2)	.6
Lund-Mackay score* before surgery, median (IQR)	15 (14-22)	19 (19-21)	.3
Perioperative oral corticosteroid taper completion, days before aspirin challenge (±SEM)	16.2 ± 0.7	15.6 ± 0.7	.6

ESS, Endoscopic sinus surgery; *FeNO*, fractional exhaled nitric oxide; *FEV1*, forced expiratory volume in 1 s; *IQR*, interquartile range.
*Lund-Mackay score: method used for radiologic staging of chronic rhinosinusitis severity. Higher score corresponds to worse disease (range 0-24).

Baseline data included measurements of fractional exhaled nitric oxide (FeNO), spirometry, and nasal inspiratory peak flow (NPF). The FeNO values were recorded by using NIOX VERO (Aerocrine AB, Morrisville, NC) according to the manufacturer's guidelines, before performing spirometry and measuring NPF. Spirometry was performed with the Puritan Bennett Renaissance II spirometer (Pleasanton, Calif) to measure FEV1. NPF was measured following the manufacturer's guidelines with an In-Check Nasal inspiratory flow device (Clement International, Ltd., Essex, UK). The best of 3 efforts was recorded for spirometry and NPF. Blood was collected at baseline for measurement of the complete blood count and eosinophil count (Sysmex XN-Series Automated Hematology Analyzer, Lincolnshire, Ill).

Urinary eicosanoid measurements

Urine was collected at baseline (before aspirin administration), and at approximately 1 to 2 hours after the onset of the aspirin-induced reaction. Urine samples were stored at −80°C and analyzed by the
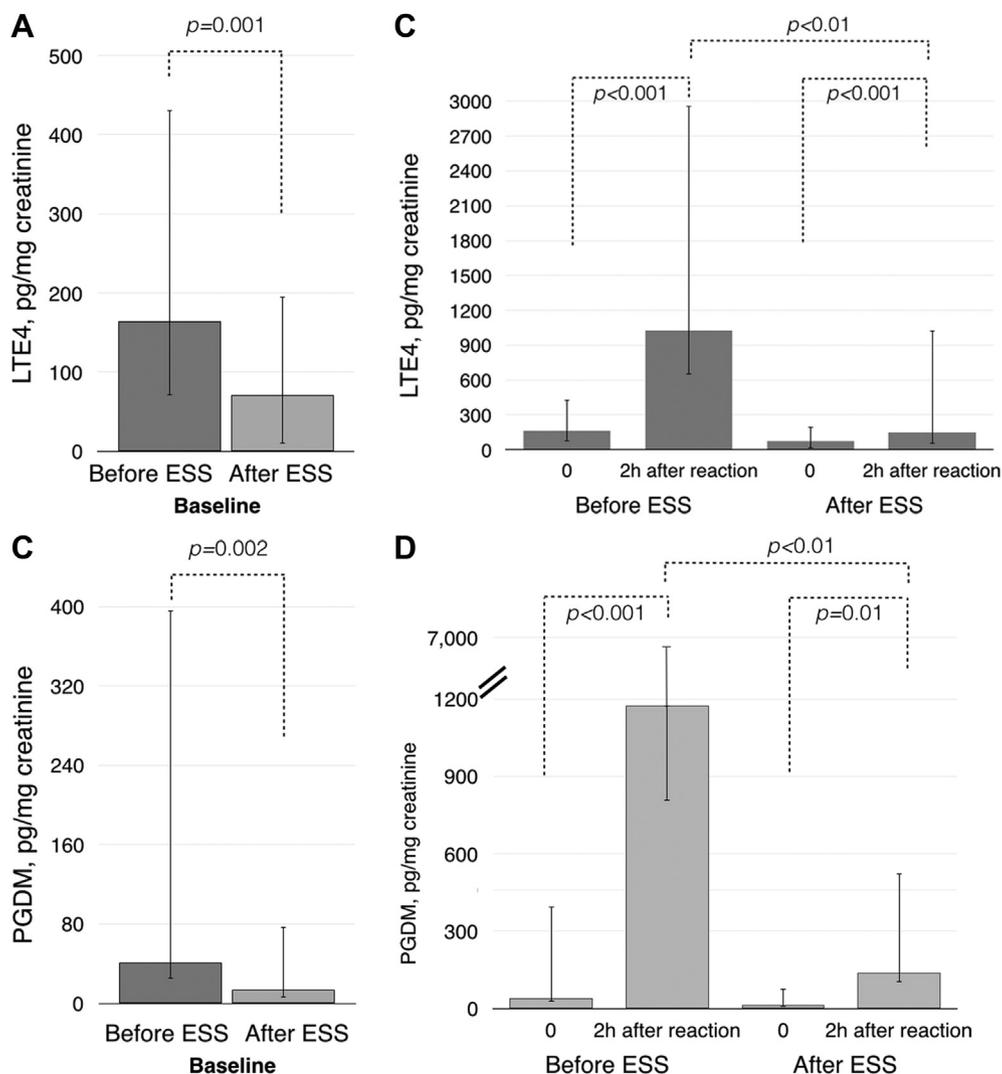
FIGURE 1. Baseline urinary LTE$_4$ levels before and after ESS (**A**) and after aspirin challenges (**B**). Baseline urinary PGDM levels before and after ESS (**C**) and after aspirin challenges (**D**). *ESS*, Endoscopic sinus surgery; *LTE$_4$*, leukotriene E$_4$; *PGDM*, prostaglandin D$_2$ metabolite.

enzyme-linked immunosorbent assay (Cayman Chemical Company, Ann Arbor, Mich) for tetranor PGDM and LTE$_4$. All measurements were made in triplicate. The results are expressed as picograms of analyte per milligram (pg/mL) of creatinine.

Plasma eicosanoid measurements

Blood samples were collected into ethylenediaminetetraacetic acid–containing collection tubes. Plasma was separated and frozen at −80°C. Samples were randomized and eicosanoids were extracted by blinded technicians. Eicosanoids were isolated by liquid:liquid extraction as previously described.[25,26] Online liquid chromatography of extracted samples was performed with an Agilent 1200 Series capillary HPLC (Agilent Technologies, Santa Clara, Calif). To measure lipoxins, we employed reverse-phase–based chiral high-performance liquid chromatography tandem mass spectrometry as previously described.[27] Concentrations of eicosanoids were measured and are reported as pg/mL.

Endoscopic sinus surgery

Patients were deemed surgical candidates if they had medically refractory disease defined as unsuccessful symptom resolution after previous medical therapy with systemic, broad-spectrum, or culture-directed antibiotics (≥2-week duration) and either topical nasal corticosteroid sprays (≥3-week duration) or at least a 5-day trial of systemic corticosteroid therapy.[28,29] ESS was performed as part of standard of care based on medical needs. All but one patient had steroid-releasing sinus implant (Propel; Intersect ENT, Palo Alto, Calif) placement during ESS.[30]

Statistical analysis

A comparison of patient characteristics between the 2 visits was made by using a paired *t* test or Wilcoxon signed-rank test (if data were non-normally distributed). All summary statistics were expressed as means ± standard error of the means or as medians and interquartile ranges (IQR). A comparison between those who reacted to the post-ESS aspirin challenge and those who did not react was made by using a 2-tailed *t* test or Wilcoxon rank-sum test (for non-normally distributed data). The proportion of asymptomatic ("silent") challenges was compared before and after ESS using the McNemar test for correlated proportions. Categorical data were analyzed by χ^2 or Fisher's exact tests, as appropriate.
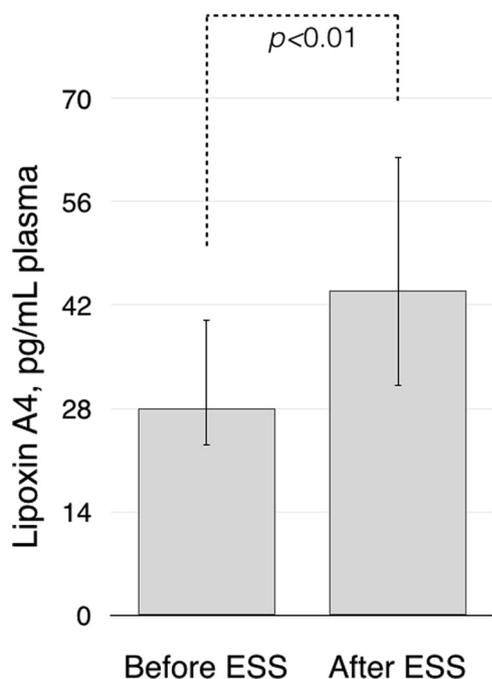
FIGURE 2. Baseline plasma lipoxin A_4 levels before and after ESS. *ESS,* Endoscopic sinus surgery.

Pearson correlation analyses were used for measuring linear dependence and expressed as Pearson coefficient. All statistical analyses were performed with STATA 14.2 software (StataCorp, College Station, Tex). *P* values of <.05 were considered significant for all analyses.

RESULTS

Twenty-eight patients with AERD were enrolled in the study. More than a half were women and the majority were either African American or Hispanic/Latino (Table I). All patients had clinical symptoms (upper and/or lower respiratory symptoms) during the hypersensitivity reaction to the challenge before ESS. After ESS, 12 of 28 patients (43%) had no clinically obvious signs of reaction (Table II, *P* < .001).

Comparison of clinical outcomes with aspirin challenge before and after ESS

There was no significant difference in baseline FEV1 % predicted before and after ESS: 83.7% predicted (±4.3) versus 83.9% predicted (±4.3), respectively (*P* = .9, Table II). As expected, there was a significant difference between baseline NPF values before and after ESS: 107 (±8.6) L/minute before versus 141 (±9.0) L/minute, respectively (*P* = .003, Table II). There was also a significant decrease in baseline FeNO from 45 (IQR 28-69) before to 28 (IQR 16-44) after ESS (*P* = .006, Table II), and in baseline peripheral blood eosinophil count from 0.7 (IQR 0.4-0.8) K/μL to 0.3 (IQR 0.1-0.5) K/μL (*P* = .003, Table II). Compared with the reactions before ESS, reactions to aspirin after ESS were less severe. In response to aspirin challenge, the FEV1 decrease was significantly greater before than after ESS: −10.0% (IQR −19.0 to −3.8) versus −8.6% (IQR −14.0 to −2.4), respectively (*P* = .02, Table II). The NPF decrease was significantly greater before

than after ESS: −26.0% (IQR −45.0 to −16.0) versus −13.0 (−20.0 to 4.0), respectively (*P* = .001, Table II). The FeNO decrease was significantly greater before ESS than after ESS: −23.0% (IQR −41.0 to −17.0) versus −13.0% (IQR −32.0 to −2.0), respectively (*P* = .04, Table II). There was no significant difference in time to onset of reaction after provoking aspirin dose: 43.0 (±5.7) minutes before versus 38.0 (±5.0) minutes after ESS in those who reacted (*P* = .5, Table II), or in the provoking dose: 80 (IQR 40-80) mg before ESS versus 80 (IQR 40-80) mg after ESS (*P* = .5, Table II).

There were no significant differences in age, gender, or racial background between patients who reacted to aspirin after ESS and those who did not (Table III), although those who had no clinically overt reaction to aspirin appeared somewhat older (50.6 ±4.4 years vs 42.5 ±3.1 years for those who reacted, *P* = .1, Table III). The decrease in FEV1 % predicted during the aspirin challenge was less in those who had no clinically obvious reaction to aspirin than in those who reacted: −5.3% (IQR −7.3 to 0) versus −10.7% (IQR −18.0 to −3.0), respectively, *P* = .04 (Table III). NPF was not significantly different between those who had no clinical reaction to aspirin compared with those who reacted: 125.0 (±17.0) L/minute versus 148.0 (±9.1) L/minute, respectively (*P* = .2, Table III). However, the decrease in NPF was significantly less in those who did not react versus those who reacted: 0 L/minute (IQR −7.1 to 6.3) versus −14.0 L/minute (IQR −21.0 to −2.3), respectively, *P* = .02 (Table III). Peripheral blood eosinophil counts were lower in those who did not react compared with those who reacted: 0.1 K/μL (IQR 0.1-0.3) versus 0.4 K/μL (0.2-0.8), respectively, *P* = .006 (Table III).

Eicosanoid changes during aspirin challenge before and after ESS

Baseline urinary LTE_4 levels were higher before ESS than after ESS: 164.0 pg/mg creatinine (IQR 93.0-267.0) versus 71.0 pg/mg creatinine (IQR 61.0-124.0), respectively (*P* = .001, Figure 1, *A*). Urinary LTE_4 levels significantly increased after aspirin challenges both before and after ESS. Before ESS, urinary LTE_4 levels increased from 164.0 pg/mg creatinine (IQR 93.0-267.0) to 1023.0 pg/mg creatinine (IQR 375.0-1933.0) (*P* < .001, Figure 1, *B*). After ESS, aspirin challenge induced a smaller increase in urinary LTE4: from 71.0 pg/mg creatinine (IQR 61.0-124.0) to 150.0 pg/mg creatinine (IQR 98.0-874.0) (*P* < .001 for the increase from baseline and *P* < .01 for the comparison of urinary LTE_4 levels after challenges before and after ESS, Figure 1, *B*).

Baseline urinary PGDM levels were also higher before ESS than after ESS: 41.0 pg/mg creatinine (IQR 16.0-355.0) versus 14.0 pg/mg creatinine (IQR 8.0-63.0), respectively (*P* = .002, Figure 1, *C*). Before ESS, urinary PGDM levels increased after aspirin challenge from 41.0 pg/mg creatinine (IQR 16.0-355.0) to 1175.0 pg/mg creatinine (IQR 368.0-5579.0) (*P* < .001, Figure 1, *D*). After ESS, aspirin challenge induced a smaller increase in urinary PGDM: from 14.0 pg/mg creatinine (IQR 8.0-63.0) to 138.0 pg/mg creatinine (IQR 37.0-385.0) (*P* = .01 and *P* < .01 for the comparison of urinary PGDM levels after challenges before and after ESS, Figure 1, *D*).

After ESS, plasma lipoxin A_4 plasma levels were significantly higher than before ESS: 44.0 pg/mL (IQR 31.0-62.0) versus 28.0 pg/mL (IQR 23.0-40.0), respectively (*P* < .01, Figure 2).
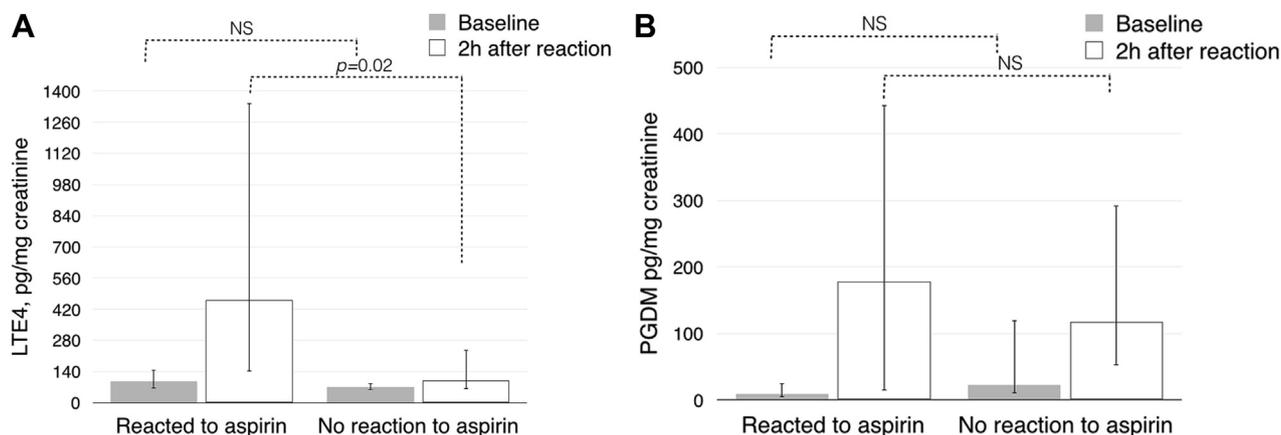
FIGURE 3. Changes in urinary LTE_4 (**A**) and PGDM (**B**) in urine during aspirin challenges after ESS in patients with and without clinical reactions to aspirin challenges. *ESS*, Endoscopic sinus surgery; *LTE_4*, leukotriene E_4; *PGDM*, prostaglandin D_2 metabolite.

Eicosanoid changes in aspirin reactors versus aspirin nonreactors

There was no significant difference in baseline urinary LTE_4 levels after ESS between patients with clinical reactions to aspirin compared with patients without clinical reaction: 95.0 pg/mg creatinine (IQR 62.0-149.0) in those who reacted versus 71.0 pg/mg creatinine (IQR 57.0-86.0) in those who did not react ($P = .2$, Figure 3, *A*). However, after aspirin challenge, patients who had a clinical reaction to aspirin had significantly higher urinary LTE_4 levels than those who did not have a reaction: 459.0 pg/mg creatinine (IQR 141.0-1344.0) versus 98.0 pg/mg creatinine (IQR 61.0-239.0), respectively ($P = .02$, Figure 3, *A*).

After ESS there was no significant difference in baseline urinary PGDM between patients who reacted and those who did not react to aspirin: 9.0 pg/mg creatinine (IQR 5.0-25.0) versus 23.0 pg/mg creatinine (IQR 10.0-120.0), respectively ($P = .09$, Figure 3, *B*). Unlike urinary LTE_4, there was no significant difference in urinary PGDM after the challenge between patients who reacted to aspirin challenge and those who did not react: 178.0 pg/mg creatinine (IQR 15.0-443.0) versus 117.0 pg/mg creatinine (IQR 53.0-291.0), respectively ($P = .8$, Figure 3, *B*).

Because the high PGD_2/PGE_2 ratio in nasal polyp tissue has been reported to be associated with nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity reactions, we analyzed the plasma PGD_2/PGE_2 ratio before and after ESS. In the whole group, there was no significant change in levels of either prostaglandin after ESS compared with levels before ESS and no significant change in the plasma PGD_2/PGE_2 ratio (data not shown). However, patients who had a clinical reaction to aspirin after ESS (reactors) had a significantly higher plasma PGD_2/PGE_2 ratio than those without reaction (nonreactors): 0.43 ($\pm$0.2) versus 0 ($\pm$0), respectively, $P = .03$ (Figure 4, *A*). To investigate this finding further, we compared plasma levels of PGD_2 and PGE_2 between reactors and nonreactors. Plasma levels of PGD_2 were significantly higher in reactors compared with nonreactors: 39.4 ($\pm$18.4) versus 0 ($\pm$0), respectively, $P = .03$ (Figure 4, *B*). The plasma levels of PGE_2 were also higher in reactors than in nonreactors: 177.8 ($\pm$44.0) versus 70.7 ($\pm$14.5), respectively, $P = .04$ (Figure 4, *C*).

Plasma lipoxin A_4 was not significantly different in patients who did not react to aspirin after ESS versus those who reacted (Figure 4, *D*).

DISCUSSION

NSAID hypersensitivity is the defining feature of AERD. This study suggests that 3 to 4 weeks after ESS, patients with AERD become less reactive to aspirin and some patients become aspirin tolerant.

Clinically, this study highlights the importance of establishing the diagnosis of AERD before ESS in patients with suspected but not confirmed AERD. On the other hand, in those with confirmed AERD, aspirin desensitization would be safer and the hypersensitivity reactions less severe after ESS. Mechanistically, the study indicates an important role that the presence of the nasal polyp tissue has in defining AERD phenotype.

Although asymptomatic ("silent") challenges and desensitizations have been reported to occur after premedication with leukotriene inhibitors, systemic corticosteroids, and/or antihistamines,[24,31] to our knowledge, this is the first report of silent challenges occurring after recent ESS. Although AERD diagnosis could be made based on historic reactions,[2,32] not all patients with AERD take NSAIDs. Therefore, some patients could be unaware of their sensitivity to NSAIDs. If undiagnosed, such patients are at risk for severe, life-threatening reactions to NSAIDs and at risk for regrowth of the nasal polyps despite multiple polyp surgeries.[24] Moreover, some patients take low-dose NSAIDs and identify themselves as nonallergic.[33] For such patients, confirmatory aspirin challenge remains an important diagnostic procedure.[33] Because more than a third of the patients in this study had silent challenges after ESS, we suggest that diagnostic aspirin challenge should be offered before the nasal polyp removal to increase its diagnostic accuracy in patients with suspected but not confirmed AERD. Aspirin challenges are an accepted diagnostic modality for AERD.[24,33] These are frequently followed by aspirin desensitization that is currently the only unique treatment available to patients with AERD.[32]

Urine and plasma levels of several biomarkers of AERD changed after ESS. There was a significant decrease in urinary LTE_4 and PGD_2—the key eicosanoids of hypersensitivity reactions during aspirin challenges. Urinary LTE_4 levels have been previously suggested as a biomarker of reaction severity,[19,21] and it was observed that LTE_4 levels decreased after ESS.[22] Interestingly, urinary LTE_4 was also proposed to be
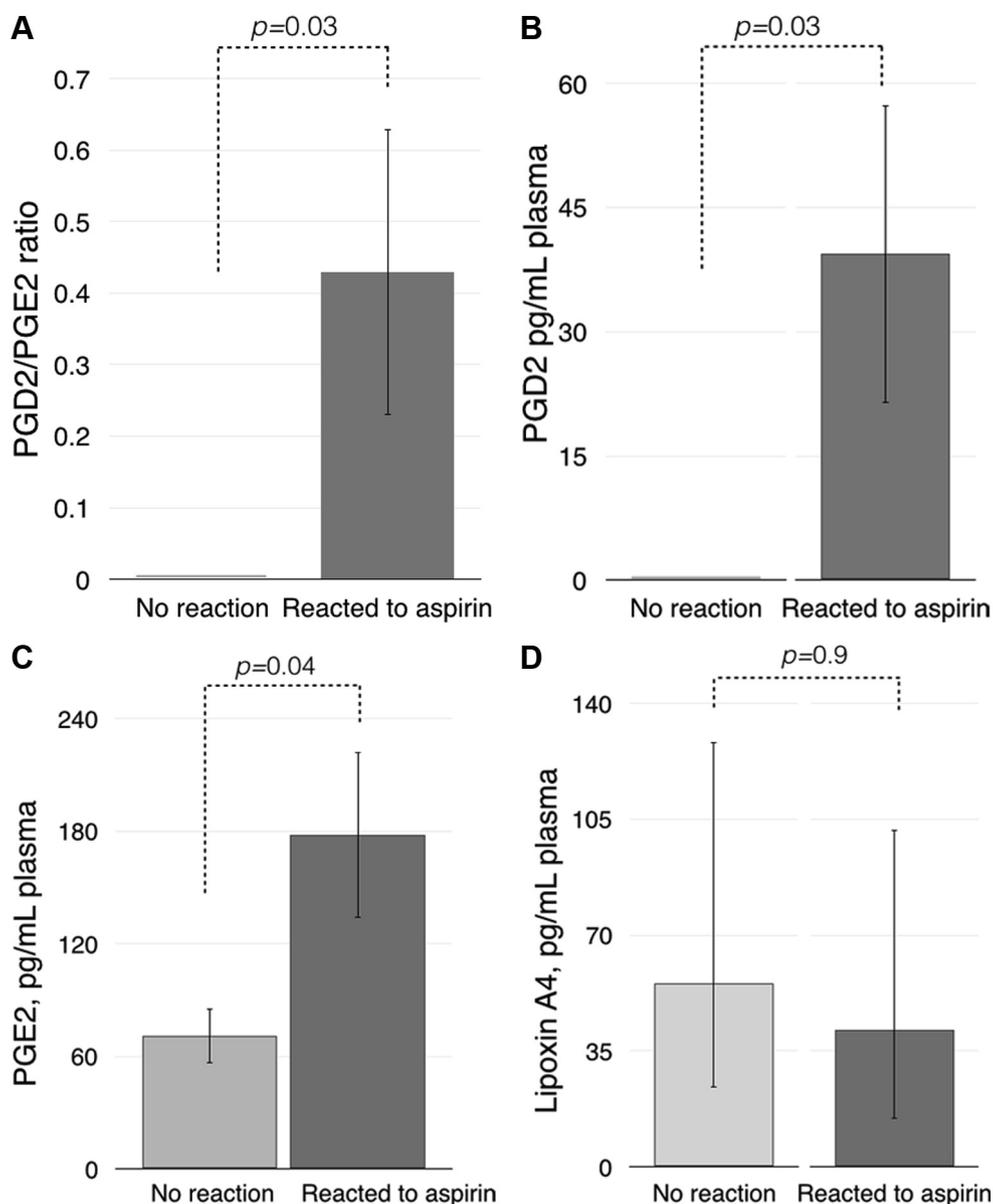
FIGURE 4. Plasma PGD_2/PGE_2 ratio (**A**), and plasma levels of PGD_2 (**B**), PGE_2 (**C**), and lipoxin A_4 (**D**) in patients with and without clinical reactions to aspirin challenges. PGD_2, Prostaglandin D_2; PGE_2, prostaglandin E_2.

a diagnostic marker of AERD.[34,35] A concentration of 166 pg/mg creatinine was found to be a reliable threshold for diagnosing aspirin hypersensitivity.[34] Notably, median LTE_4 urinary levels in this study population at baseline (before ESS) were close to the proposed diagnostic value, 164 pg/mg creatinine. However, urinary LTE_4 levels significantly decreased after surgery. It should be emphasized that the diagnostic value of LTE_4 for identifying aspirin hypersensitivity has higher sensitivity before ESS. LTE_4 levels between 67 and 80 pg/mg creatinine were reported as normal.[36-38] The median urinary LTE_4 concentration after ESS in this study was within the normal range (71 pg/mg creatinine), and was associated with either a less severe or a complete lack of a clinical reaction to aspirin during challenges. Although urinary LTE_4 is an accurate

diagnostic marker for aspirin intolerance in patients with asthma,[35] it is important to note that LTE_4 levels become less reliable after ESS. Thus, LTE_4 urinary levels should be considered as a diagnostic marker for AERD in patients in whom nasal polyps are present and who do not have a recent ESS. Both higher peripheral blood eosinophil counts and a greater increase in urinary LTE_4 levels during challenge were associated with symptomatic challenges after ESS. Thus, higher peripheral eosinophil counts could be predictive of a greater increase in urinary LTE_4 levels and higher probability of experiencing a hypersensitivity reaction during aspirin challenge. Baseline median FeNO values after ESS were significantly lower than before ESS (Table II). This may imply that the eosinophilic inflammation in the lungs decreased after

surgery and/or that nasal polyp eosinophilia contributes to higher FeNO values when polyps are present. Although it did not reach statistical significance, the baseline FeNO value and the decrease in FeNO levels after aspirin challenges were somewhat lower in patients with silent challenges after ESS compared with patients who reacted (Table III). As reported previously, a greater FeNO decrease during aspirin challenge in patients with AERD was associated with a greater decrease in FEV1.[20]

After ESS, there was a significant increase in plasma lipoxin A_4 levels. Higher lipoxin A_4 levels and higher PGE_2 levels are associated with less severe asthma.[39,40] This study also suggests that having a lower plasma PGD_2/PGE_2 ratio is associated with a lack of a clinical reaction to aspirin after nasal polyp removal, pointing toward a possible link between a high plasma PGD_2/PGE_2 ratio and NSAID hypersensitivity in AERD. Both eicosanoids are produced from a common precursor PGH_2.[41] In nasal polyp tissue, PGD_2 is primarily produced by mast cells,[13] and polyp removal may diminish this source of PGD_2. However, some patients who remain aspirin reactive maintain elevated PGD_2/PGE_2 ratios. It is possible that PGD_2 synthase (PGDS) is available in other respiratory tissues after the excision of nasal polyps that are high in PGDS.[13] Elevated PGD_2 may be a causative factor in AERD reactivity, as higher PGD_2 plasma levels are associated with reduced eosinophil apoptosis and with eosinophilic inflammation in patients with chronic rhinosinusitis.[42]

Limitations of this study are lack of placebo and randomization preceding aspirin challenges before and after ESS. In addition, repeating challenges several months after surgery have been of clinical interest to reconfirm reproducibility of the results, although a previous study reported 97.6% reproducibility of aspirin challenges in patients with AERD and intact nasal polyps.[43] Moreover, correlating outcomes from aspirin challenges and the status of the nasal polyp recurrence might further confirm our hypothesis that the presence of nasal polyps influences aspirin-induced hypersensitivity reactions during challenges. This study suggests increased safety of aspirin challenges within 3 to 4 weeks after ESS (notably, some patients had evidence of polyp regrowth at this time). However, polyp recurrence could reduce safety of aspirin challenges and desensitizations at later times. Despite these limitations, our study has several strengths including each patient serving as his/her control, a unique representation of minority patients who constituted 75% of the study population, and correlation of the clinical findings and biomarker levels.

In summary, our study presents 2 novel findings in AERD: (1) sinus surgery is associated with characteristic changes in plasma and urine eicosanoids and with a subsequent decrease in reaction severity to aspirin challenges; (2) diagnostic accuracy of oral graded aspirin challenge for AERD is greater if attempted before ESS than 3 to 4 weeks after ESS. In patients with confirmed AERD, aspirin desensitization would be safer and the hypersensitivity reaction less severe 3 to 4 weeks after ESS. It is important to emphasize that aspirin challenges and desensitizations should be conducted by physicians who have appropriate training in protocol administration and management of allergic reactions and anaphylaxis.

Clinical symptoms during challenges are strongly linked to changes in several plasma and urine eicosanoids and peripheral blood eosinophils. These associations appear to depend on the presence of the nasal polyp tissue in patients with AERD. Therefore, nasal polyp tissue studies might be particularly informative in elucidating the mechanism of AERD.

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