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Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease

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Abstract

Background—A large percentage of patients with aspirin exacerbated respiratory disease (AERD) report the development of alcohol-induced respiratory reactions, but the true prevalence of respiratory reactions caused by alcoholic beverages in these patients was not known.

Objective—We sought to evaluate the incidence and characteristics of alcohol-induced respiratory reactions in patients with AERD.

Methods—A questionnaire designed to assess alcohol-induced respiratory symptoms was administered to patients at Brigham and Women's Hospital and Scripps Clinic. At least 50 patients were recruited into each of four clinical groups: 1) patients with aspirin challenge-confirmed AERD, 2) aspirin-tolerant asthmatics (ATA), 3) aspirin-tolerant patients with chronic rhinosinusitis (CRS), and 4) healthy controls. Two-tailed Fisher's exact test with Bonferroni corrections were used to compare the prevalence of respiratory symptoms between AERD and other groups, with $P \leq 0.017$ considered significant.

Results—The prevalence of alcohol-induced upper (rhinorrhea/nasal congestion) respiratory reactions in patients with AERD was 75%, compared to 33% in ATA, 30% in CRS, and 14% in healthy controls ($P<0.001$ for all comparisons). The prevalence of alcohol-induced lower (wheezing/dyspnea) respiratory reactions in AERD was 51%, compared to 20% in ATA, and 0%

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in both CRS and healthy controls ($P<0.001$ for all comparisons). These reactions were generally not specific to one type of alcohol and often occurred after ingestion of only a few sips of alcohol.

Conclusion—Alcohol ingestion causes respiratory reactions in the majority of patients with AERD and clinicians should be aware that these alcohol-induced reactions are significantly more common in AERD than in aspirin-tolerant controls.

Keywords

Samter's Triad; Aspirin Exacerbated Respiratory Disease; AERD; Aspirin Intolerant Asthma; Aspirin triad; Non-steroidal anti-inflammatory drugs; Asthma; Alcohol; Wine; Leukotriene

Introduction

Aspirin Exacerbated Respiratory Disease (AERD) is characterized clinically by the triad of asthma, recurrent nasal polyposis, and hypersensitivity to cyclooxygenase (COX)-1 inhibitors.[1] This asthma subtype accounts for 5%–10% of adult asthmatics,[2] yet represents a disproportionately high proportion of severe asthma cases[3] and can be difficult to diagnose and treat. Formal aspirin challenges are required for definitive diagnosis of AERD,[10] in part because self-reported aspirin sensitivity is not reliably predictive,[11–14] and because many asthmatics do not use nonsteroidal anti-inflammatory drugs regularly and may be unaware of their hypersensitivity.[15]

Alcohol-induced respiratory reactions have been reported with rates varying from 20–40% in asthmatics[4–6] and occasionally in patients with rhinitis[7] and in the general population.[8] However, the majority of our patients with AERD described experiencing respiratory reactions following alcohol ingestion, with a seemingly greater prevalence than that known for other patient groups, and several patients with AERD reported that alcohol had induced frightening lower respiratory symptoms and acute asthma exacerbations. Though an association between aspirin sensitivity and alcohol-induced reactions in asthmatics has been suggested,[4, 5, 9] these reactions have never been characterized in a well-phenotyped group of patients with aspirin challenge-confirmed AERD.

Additionally, we found no published data regarding the characteristics of alcohol-induced respiratory reactions in patients with AERD. To address these issues and explore the potential mechanisms underlying alcohol-induced reactions, we designed a questionnaire to investigate the incidence and frequency of reactions, and to examine details including time to onset of reactions, amount of alcohol required to induce reactions, and type of alcohol most likely to cause reactions. We offered participation in this multi-centered questionnaire-based study to aspirin challenge-confirmed patients with AERD, and to three clinically-defined control groups: patients with aspirin-tolerant asthma (ATA), chronic rhinosinusitis (CRS), and healthy controls. Our findings show that patients with AERD report a strikingly high prevalence of both upper and lower respiratory reactions induced by alcohol; this observation furthers the clinical characterization of AERD and may suggest its diagnosis.

Methods

Patients and human subject characterization

Study participants between the ages of 21 and 75 were recruited from the Brigham and Women's Hospital Allergy and Asthma and Otolaryngology clinics, and from the Scripps Clinic's Allergy and Asthma clinic. Subjects completed surveys in the form of printed questionnaires or through REDCap™, an online data-gathering and analysis tool; all participants from Scripps Clinic completed printed questionnaires. Due to limitations in the questionnaire protocol as approved at the Scripps Clinic, demographic information and clinical information from the medical record were only collected from subjects recruited at the Brigham and Women's Hospital. Recruitment at both centers began in April 2012 and concluded in May 2013.

Participants were allocated into four clinical groups: 1) patients with AERD whose diagnosis was confirmed after a respiratory reaction was documented during supervised challenge to aspirin, 2) patients with ATA, 3) nonasthmatic patients with CRS and 4) healthy controls. Patients who had never consumed alcohol and those diagnosed with cystic fibrosis were excluded from participation. All subjects with ATA had physician-diagnosed asthma and had taken a COX-1 inhibitor in the past 6 months without adverse reaction. Subjects with CRS were physician-diagnosed based on published guideline criteria,[16] had taken a COX-1 inhibitor in the past 6 months without adverse reaction, and had no history of asthma in adulthood. Subjects were excluded from the healthy control group if they had a history of asthma, rhinitis, AERD, or sensitivity to any COX-1 inhibitor.

The human subjects Institutional Review Boards of the Brigham and Women's Hospital (protocol 2012-P-000175) and the Scripps Clinic (protocol IRB-12-5856) approved the study, and all subjects provided written consent in accordance with the Declaration of Helsinki.

Questionnaire and study design

The complete questionnaire is available in Figure E1 of the Online Repository. The number of questions was limited to 18 to avoid bias from responder fatigue. The questionnaire confirmed the presence or absence of physician-diagnosed asthma, nasal polyposis, CRS, and AERD. A history of respiratory reactions to alcohol was evaluated with the question, "has drinking alcohol ever triggered any of the following symptoms? (check all that apply)", with the following possible answers: "stuffy nose/nasal congestion; runny nose; shortness of breath; wheezing; none of the above". Upper respiratory symptoms were defined as positive answers to either of the first two questions, and lower respiratory symptoms were defined as positive answers to either of the latter two. Respondents who checked any of the above respiratory symptoms were then asked several questions to detail their alcohol-induced reactions in regards to time to onset, frequency, specificity to alcohol type, quantity of alcohol required to provoke reactions, and whether they had cut down their alcohol consumption due to the development of respiratory reactions. Subjects with AERD who had been desensitized to aspirin and continued with daily high-dose aspirin treatment were asked whether or not aspirin therapy blunted alcohol-induced reactions. Susceptibility to common

environmental irritants, a self-assessment of their sense of smell, use intranasal steroids, and number of lifetime nasal polypectomies were inquired as measures of baseline respiratory disease. For participants from Brigham and Women's Hospital, asthma severity of subjects with AERD was compared to that of subjects with ATA using Asthma Control Test™ (ACT™) scores(range 5–25, with >19 indicating well-controlled asthma) and forced expiratory volume in 1 second (FEV1) values from office spirometry.

Statistical analysis

A two-tailed Fisher's exact test with Bonferroni correction was used to compare the prevalence of respiratory symptoms between AERD and other groups, with $P \leq 0.0125$ considered significant. This statistical tool was also used to compare gender and racial/ethnic compositions of the study groups, prevalence in reaction rates in men vs. women within each group, alcohol types that provoked respiratory reactions most forcefully, quantity of alcohol required to provoke reactions, time to onset, frequency of reactions, and inter- and within group comparisons between reactions to alcohol and reactions to other exposures. An unpaired t-test compared the percent predicted FEV1 and ACT™ scores between subjects with AERD and those with ATA, with $P \leq 0.05$ considered significant.

Results

Demographics and characteristics of respiratory disease

A total of 213 study participants were recruited; their demographic data are summarized in Table I. There were no statistical differences in racial/ethnic backgrounds or age of patients in each group. Consistent with previous reports, [3] the AERD patient group had a slight female predominance. There was no significant difference in rates of alcohol-induced reactions in female vs. male patients in any clinical group. Asthma severity in Brigham and Women's Hospital's study subjects, compared using baseline percent predicted FEV1 and ACT™ scores whenever available from the medical record, was not statistically different between asthmatics with ATA and those with AERD. The percentage of subjects diagnosed with nasal polyps (NPs) is also reported, and as expected, nearly all patients with AERD had NPs.

Prevalence of alcohol-induced respiratory symptoms

The prevalence of upper and lower alcohol-induced respiratory reactions reported by each patient group is summarized in Figure 1. To address the concern that nasal polyposis may confound differences reaction rates between groups, an additional clinical subgroup was defined to include all aspirin-tolerant respondents with NPs, derived from the ATA and CRS groups; no healthy control patients had NPs. Upper respiratory reactions to alcoholic beverages were reported by 75% of respondents with AERD, in contrast to 33% of ATA, 30% of CRS, 40% of aspirin-tolerant respondents with NPs and 14% of healthy controls ($P<0.001$ for the above four comparisons, Fig 1,*A*). Lower respiratory reactions were also significantly more common in patients with AERD (51%) versus patients with ATA (20%) and aspirin-tolerant patients with NPs (10%); no nonasthmatic subject (CRS and healthy controls) reported lower respiratory reactions to alcohol ($P<0.001$ for the above four comparisons, Fig 1,*B*). Respiratory reactions of either type, upper and/or lower, were more

frequently reported by AERD patients (83%), than by those with ATA (43%), CRS (30%), aspirin-tolerant patients with NPs (43%), or healthy controls (14%) ($P<0.001$, Fig 1,*C*). These reported reaction rates were not statistically different within any patient group between those subjects surveyed at the Scripps Clinic and those surveyed at the Brigham and Women's Hospital.

Of respondents who reported alcohol-induced respiratory reactions, 73% of those with AERD cut down alcohol consumption or quit after developing these reactions, and 57% of aspirin-tolerant asthmatics did so. This difference was not statistically significant ($P=0.18$).

Characterization of respiratory reactions to alcoholic beverages

Participants who reported alcohol-induced respiratory reactions were asked to identify which type of alcohol elicited reactions most forcefully. Responses were similar across patient groups (Fig 2). Although many patients identified red wine as the most forceful trigger, no single alcohol type was determined to be the main culprit, and >1/3 of subjects with AERD and ATA reported that all alcohol types were equivalent triggers for respiratory reactions.

The quantity of alcohol needed to elicit respiratory reactions was similar between AERD and ATA, and was ≤3 glasses for almost all participants; the majority of patients with AERD (51%) reported that 'a few sips' would elicit their reactions (Table II). The majority of respondents with both AERD and ATA developed their reactions within ≤1 hour of alcohol intake (84% and 78%, respectively) (Table III), and reported doing so 'more than half the time' or 'all the time' they drink alcohol in 65% and 61% of cases, respectively (data not shown). In addition, of the respondents with AERD who had begun high-dose daily aspirin therapy and had re-tried drinking alcohol after starting aspirin, 63% reported an improvement in alcohol-induced respiratory reactions since starting this therapy (data not shown). To assess whether reactivity to alcohol was associated with reactivity to other types of exposures, and therefore associated with general respiratory sensitivity, participants were asked about respiratory reactions to cold or hot air, use of toothpaste, beef consumption, cold or hot beverages, or 'any'. The prevalence of reactions to these exposures was similar across all four patient groups, and also similar for all study groups when patients were subcategorized into alcohol responders and non-responders, without statistically significant differences noted (data not shown).

Relationship between severity of aspirin-induced reactions and alcohol-induced reactions in patients with AERD

We sought to determine whether a relationship existed between the severity of aspirin-induced reactions and the severity of alcohol-induced reactions in patients with AERD. Nasal symptoms involving only the upper respiratory tract are generally considered to be mild and less intense than potentially life-threatening lower respiratory symptoms of wheezing and shortness of breath, and therefore patients who developed lower respiratory symptoms were defined as having "severe" reactions. The 23 AERD patients for whom clinical data from their aspirin challenge was available were subdivided into those who developed only upper respiratory reactions (n=10) and those who developed lower

respiratory reactions (including a fall of ≥15% in FEV1 during aspirin challenge (n=13)); their likelihood of reacting to alcohol was compared. Patients who developed only upper respiratory reactions or no reactions to alcohol were statistically significantly more likely to have developed only upper respiratory reactions to aspirin, and patients who developed lower respiratory reactions to alcohol were statistically significantly more likely to have developed lower respiratory reactions during aspirin challenge (Table IV). The odds of developing a lower respiratory reaction to aspirin was 8.2 fold greater (95% CI of 1.2–59.0) for subjects with AERD who had developed lower respiratory reactions to alcohol compared to those who had developed upper respiratory only or no reactions to alcohol.

Discussion

Previous studies have shown that respiratory reactions may result from alcohol consumption, especially in asthmatics. In a cross-sectional study in 2008 with 4,066 participants, Linneberg et al. found the rates of alcohol-induced upper and lower respiratory reactions to be 7.6% and 3.2%, respectively. These reactions were more prevalent in asthmatics, with 17.5% reporting upper and12.9% reporting lower respiratory reactions. Other studies have reported similar rates of alcohol-induced respiratory reactions in asthmatics, ranging from 21% to 40%.[4–7] However, less was known about alcohol-induced respiratory reactions in patients with AERD. The only previous study that investigated both alcohol-induced reactions and AERD was a survey by Vally et al. of 366 asthmatic subjects, of whom 11% self-reported aspirin-induced asthma.[4] That study found that 33% of asthmatics reported alcohol-induced respiratory exacerbations and noted increased rates in patients with self-reported aspirin-induced asthma, as the odds ratio for alcohol-induced respiratory reactions was 2.98 for this asthmatic subgroup. In order to more specifically examine this phenomenon, we sought to investigate the rates and characteristics of alcohol-induced reactions in well-phenotyped patients with AERD and in aspirin-tolerant controls.

A large portion of the asthmatics who completed our survey reported the onset of respiratory reactions upon alcohol ingestion. Our finding, that 43% of patients with ATA developed upper and/or lower alcohol-induced respiratory reactions, was similar to rates described for asthmatics in other studies.[4, 6] However, we found that 83% of patients with AERD developed alcohol-induced respiratory reactions, which is strikingly higher than the rates found in any other clinical group and is in keeping with the anecdotal evidence from our clinic patients. Our data did not suggest that this high reaction rate was due to differences in severity of baseline pulmonary disease, as there was no difference in asthma severity or control between patients with AERD and ATA, as measured by ACT™ score and FEV1. These high reaction rates were also not explained by the presence of NPs, as the reaction rates in aspirin-tolerant patients with NPs was about half that of AERD patients with NPs. There was a slight female predominance in our AERD population, paralleling the findings of previous groups,[3] though there was no gender-specific difference in alcohol-induced reaction rates in either aspirin-tolerant or AERD patients. As respiratory reactions began for most respondents within minutes of drinking even very small amounts of alcohol, alcohol intoxication is also unlikely to be the causative mechanism of these reactions. However, the <30 minute time-to-onset of reaction may correlate with peak blood alcohol levels, as peak alcohol levels are often achieved within 30 minutes of ingestion.[18] Sulfite hypersensitivity

also exists in some asthmatics[19, 20] and although one-third of our respondents with AERD reported that red wine was the alcohol type causing the most forceful respiratory reactions, most patients found that all alcohols incited reactions, even those with little to no sulfites. Additionally, studies comparing broncho constriction induced by wine with high vs. low sulfite content have not found any difference between the two,[21–23] suggesting that alcohol itself, and not an additive, is the culprit for these reactions. Sensitivity to alcohol is common in Asian populations due to a polymorphism in acetaldehyde dehydrogenase, and patients classically present with facial flushing and occasionally respiratory symptoms.[24] In Western populations however, this polymorphism is infrequent and thus unlikely to be the mechanism underlying the reactions described by our AERD patients.

One consistent finding in AERD is that patients have elevated cysteinyl leukotrienes levels at baseline, reflected by the detection of the end metabolite leukotriene (LT)E_4 in urine, which increases further during reactions to aspirin.[25] Cysteinyl LTs are powerful broncho constrictors and main effectors of aspirin-induced reactions, but neither the cellular source of cysteinyl LTs nor the mechanisms of aspirin-induced increase are known. The mechanisms underlying the alcohol-induced respiratory reactions in AERD patients are also unknown, but considering the dominant role that cysteinyl LTs play in AERD pathogenesis, we suspect that a similar LT-dependent mechanism may underlie their alcohol-induced respiratory reactions. Moreover, the baseline level of urinary LTE_4 is currently the only biomarker available to clinicians for predicting the severity of aspirin-induced reactions in AERD patients AERD.[26] However, in this study we found that the severity of aspirin-induced reactions (observed in clinic during aspirin challenges) positively correlated with the severity of alcohol-induced reactions (self-reported by survey respondents). Given that urinary LTE_4 measurements are mostly limited to research centers, this new finding may aid clinicians in predicting the severity of reactions during aspirin challenges, and in counseling patients about consequences of alcohol consumption.

Indeed, excessive ethanol consumption by healthy individuals has been shown to increase urinary LTE_4 excretion, presumably reflecting elevated systemic cysteinyl LT levels due to ethanol-induced inhibition of LT catabolism.[27] Although these alcohol-induced urinary LTE_4 elevations were may not cause reactions in healthy individuals, asthmatic patients are known to be 200-fold more sensitive to LTE_4-induced broncho constriction than nonasthmatics,[28] and patients with AERD are 16-fold further more sensitive to broncho constriction by LTE_4 than aspirin-tolerant asthmatics.[29] It is suspected that this hyper responsiveness to LTE_4 in AERD is due to over expression of a yet undiscovered LTE_4-specific receptor, but to date no such receptor has been reported. Interestingly, 63% of respondents with AERD on high-dose daily aspirin therapy who had re-tried drinking alcohol after starting aspirin reported an improvement in alcohol-induced respiratory reactions, suggesting that high-dose aspirin therapy may attenuate alcohol hyper responsiveness in AERD patients.

This study has several limitations, principally those inherent in survey research and its liability to patient recall and response bias. In addition, due to the relatively small population of subjects with AERD available for study, our questionnaire was not able to be formally validated. Therefore it was subjected to screening by our multiple authors for re-test

reliability and linguistic validity before IRB submission and administration to study participants, and was based in part on previously published questionnaires[4–8]. Additionally, our survey queried susceptibility to environmental exposures as a measure of interpretability and specificity and we found similar reaction rates to environmental exposures among study participants (excluding healthy controls), suggesting that our survey questions on respiratory reactions to alcohol were correctly interpreted by respondents, and that respiratory reactions to alcohol are specific. For future studies, a double-blind, placebo-controlled alcohol challenge study would be optimal to circumvent our study's limitations and clarify the mechanisms underlying our findings.

In this study we have thoroughly examined the effects of alcoholic drinks on the development of respiratory reactions in AERD patients and have found that alcoholic beverages are common and occasionally dangerous triggers for respiratory reactions in these patients. This finding may aid clinicians in the suspicion of AERD, and suggests that clinicians should warn their patients with AERD about the potential for alcohol-induced respiratory reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AERD	Aspirin Exacerbated Respiratory Disease
COX	cyclooxygenase
ATA	aspirin-tolerant asthma
LT	leukotriene
CRS	chronic rhinosinusitis
NPs	nasal polyps

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Highlights box

What is already known about this topic?

Alcohol-induced respiratory reactions are common in asthmatics and associated with aspirin sensitivity, but their prevalence and characteristics in patients with AERD are unknown. (23 words)

What does this article add to our knowledge?

The majority of patients with AERD experience alcohol-induced reactions, and these are more severe than in aspirin-tolerant patients. The severity of reaction to aspirin correlates to the severity of reaction to alcohol. (32 words)

How does this study impact current management guidelines?

A history of respiratory reactions upon alcohol ingestion may aid in the suspicion of AERD; clinicians should warn their patients about this possibility. (23 words) 2.

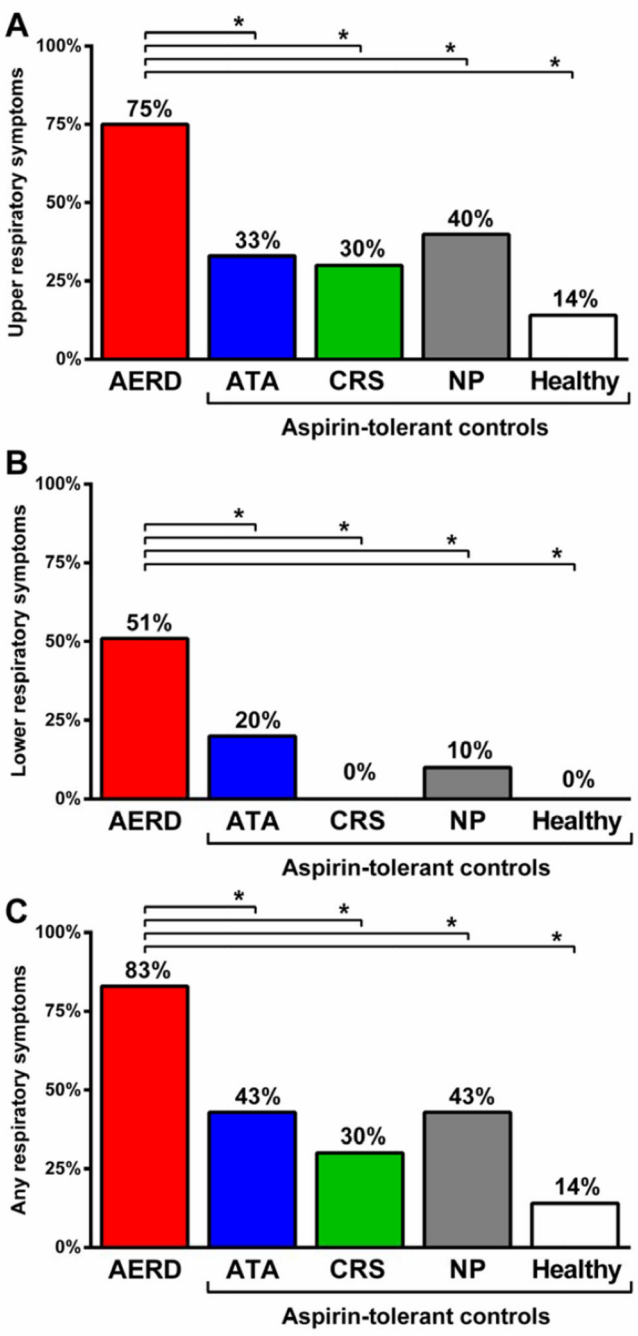

Figure 1.

Prevalence of alcohol-induced respiratory symptoms. Rates of alcohol-induced (A) upper, (B) lower, and (C) upper and/or lower respiratory reactions among survey respondents with AERD, ATA, CRS, aspirin-tolerant subjects with nasal polyps (NP), and healthy controls. *P<0.001 for all four rates compared to the AERD group in A-C.

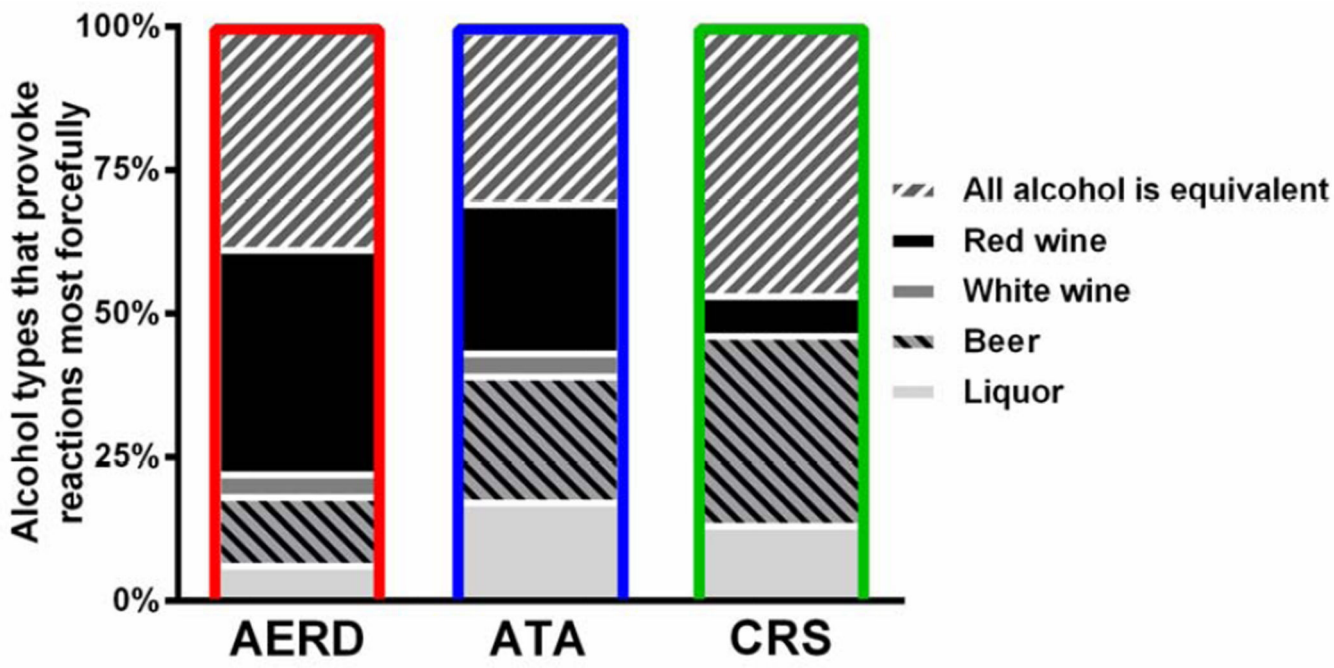

Figure 2.

Alcohol types that provoke reactions most forcefully. Among participants who reported alcohol-induced respiratory reactions, the type of alcohol they identified as eliciting reactions most forcefully is shown. Significantly more patients with AERD (39%) identified red wine as the most forceful trigger than did patients with CRS (7%) (P=0.02). No other comparisons were significantly different across patient groups.

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Table I

Demographics and respiratory disease characteristics*

	AERD	ATA	CRS	Healthy controls	p value
Total Number (BWH, Scripps)	**59** (23, 36)	**54** (28, 26)	**50** (36, 14)	**50** (15, 35)	
Median age* (range, in years)	**45** (31–66)	**40.5** (23–73)	**44.5** (21–75)	**34** (22–71)	0.06
Gender* (% female)	70%	54%	42%	60%	0.29
Race/Ethnicity*					
Caucasian	20/23	22/28	28/36	12/15	
Hispanic	1/23	3/28	5/36	2/15	
Asian	1/23	2/28	2/36	1/15	
Declined to answer	1/23	1/28	1/36		
FEV1 (mean % predicted)* (N, range)	**86%** (23, 58–114%)	**85.5%** (22, 60–123%)	N/A	N/A	0.92
Mean ACT™ score* (N, range)	**17** (19, 13–25)	**21** (21, 14–25)	N/A	N/A	0.57
Presence of Nasal Polyps (percent: BWH, Scripps)	100%, 97%	25%, 31%	50%, 64%	0%, 0%	

BWH: Brigham and Women's Hospital, FEV1: forced expiratory volume in 1 second, ACT™: Asthma Control Test, AERD: aspirin exacerbated respiratory disease, ATA: aspirin tolerant asthma, CRS: chronic rhinosinusitis, N/A: not applicable or available.

*Age, gender, race/ethnicity, FEV1 and ACT™ score data apply only to survey respondents from BWH

Table II

Quantity of alcoholic beverage required to provoke reactions[□]

Dose	AERD	ATA	p value
A few sips	25/49 (51%)	9/23 (39%)	0.45
1–3 glasses	21/49 (43%)	11/23 (48%)	0.8
> 3 glasses	3/49 (6%)	3/23 (13%)	0.38
3 glasses or less	46/49 (94%)	20/23 (87%)	0.38

AERD: aspirin exacerbated respiratory disease, ATA: aspirin tolerant asthma

□Number of those reporting dose of alcohol needed to trigger respiratory reactions over number of those who experience respiratory reactions with alcoholic beverages, percentage in parenthesis.

Table III

Time to onset of respiratory reactions after ingestion of alcohol[□]

Time	AERD	ATA	p value
< 15 minutes	16/49 (33%)	6/23 (26%)	0.78
15 minutes to 1 hour	25/49 (51%)	12/23 (52%)	1
1 hour or less	41/49 (84%)	18/23 (78%)	0.74
1–24 hours	8/49 (16%)	5/23 (22%)	0.74

AERD: aspirin exacerbated respiratory disease, ATA: aspirin tolerant asthma

□Number of those reporting time of onset of respiratory reactions after alcohol ingestion over number of those who experience respiratory reactions with alcoholic beverages, percentage in parenthesis.

Table IV

Correlation of aspirin-induced respiratory reactions with alcohol-induced respiratory reactions in subjects with AERD

		Reactions during aspirin challenge		
		Only upper respiratory reactions	**Lower respiratory reactions**	**p value**
Reactions to alcoholic beverages	Upper respiratory or no reactions	6/10 (60%)	2/13 (15%)	
	Lower respiratory reactions	4/10 (40%)	11/13 (85%)	**0.04**