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Changes in bronchial hyperresponsiveness following high- and low-sulphite wine challenges in wine-sensitive asthmatic patients

H. Vally^{*†‡}, P. J. Thompson^{*†} and N. L. A. Misso^{*†}

^{*}Lung Institute of Western Australia (Inc.), Centre for Asthma, Allergy and Respiratory Research, Perth, Australia, [†]Cooperative Research Centre for Asthma, The University of Western Australia, Perth, Australia and [‡]National Centre for Epidemiology and Population Health, ANU College of Medicine and Health Sciences, The Australian National University, Canberra ACT 0200, Australia

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Summary

Background Previous studies suggest that challenge of most wine-sensitive asthmatic patients may not result in a reduction in forced expiratory volume in 1 s (FEV₁).

Objective The aim of this study was to assess whether changes in bronchial hyperresponsiveness (BHR) occur following wine challenge of asthmatic patients who report sensitivity to wine, and whether such changes could help clarify the role of sulphite additives in wine-induced asthmatic responses.

Methods Eight self-reporting wine-sensitive asthmatic patients completed double-blind challenges with high- and low-sulphite wines on separate days. FEV₁ and histamine PC₂₀ were measured before and after consumption of 150 mL of wine.

Results None of the eight subjects demonstrated a clinically significant ($\geq 15\%$) reduction in FEV₁ following challenge with either high- or low-sulphite wine. In contrast, one patient demonstrated clinically significant increase in BHR following challenge with both high- and low-sulphite wines, and a smaller increase in BHR following placebo challenge. A second patient showed a significant increase, while another showed a significant decrease in BHR following challenge with low-sulphite wine. A fourth patient showed borderline increases in BHR following challenge with both high- and low-sulphite wines.

Conclusions Although changes in BHR, in the absence of reductions in FEV₁, were observed in some asthmatic patients following wine challenge, these changes were not consistent with a single aetiology. Consequently, this study did not support a major role for the sulphite additives in wine-induced asthmatic responses in the patients studied. The aetiology of wine-induced asthma is likely to be complex and appears to vary among individuals who are sensitive to these drinks.

Keywords asthma, bronchial hyperresponsiveness, challenge, sulphite, wine

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Correspondence:

Dr Hassan Vally, National Centre for Epidemiology and Population Health, The Australian National University, Canberra, ACT 0200, Australia.
E-mail: Hassan.Vally@anu.edu.au

Introduction

Recent epidemiological studies suggest that wine consumption may be associated with a worsening of asthma symptoms in as many as 30% of asthma patients [1–3]. However, attempts to better understand this phenomenon by challenging self-reporting wine-sensitive asthmatics in a clinical setting have been hampered by a lack of positive responses [4–6]. A possible explanation is that conventional challenges performed in a clinical setting may not result in a reduction in forced expiratory volume in 1 s (FEV₁) in most wine-sensitive asthmatic subjects. Anec-

dotal data from our laboratory and from others are consistent with the hypothesis that cofactors play an important role in wine sensitivity [7, 8]. Thus, some individuals may react to wine only when their asthma has been aggravated by exposure to other irritants or triggers in the environment, or conversely, wine consumption may increase reactivity to other irritants or triggers. In either case, challenge with wine alone, under controlled conditions, may not elicit a measurable change in FEV₁.

Epidemiological data from one study suggest that the sulphite additives in wine may play an important role in

wine-induced asthmatic responses [1]. That Australian study demonstrated a significant association between wine-induced asthma and asthmatic reactions to sulphite-containing foods, providing indirect evidence of a role for the sulphite additives. However, attempts to verify this by challenge studies have met with limited success [6, 9], and in general it has not been possible to confirm sensitivity to the sulphite in wine among asthmatics who provided compelling histories of wine sensitivity. Confirmation that sulphite additives, at the levels and in the chemical form found in wine, are able to elicit asthmatic responses would be an important step towards understanding the phenomenon of wine-induced asthma. Conversely, if these additives do not play a major role in wine-induced asthma, then efforts need to be directed towards investigating other components of wine that may be involved [3, 10, 11].

Previous studies suggest that consumption of food and drinks by sensitive individuals results in increased bronchial hyperresponsiveness (BHR), in the absence of measurable reductions in FEV₁ [12–14]. However, there have been no previous measurements of BHR following wine consumption. In this study, we explored the possibility that wine consumption may induce changes in bronchial hyperresponsiveness among asthmatic patients who report sensitivities to wine. In addition, we sought evidence for the involvement of sulphite additives in wine-induced asthmatic responses.

Methods

Subjects

Thirteen patients with stable asthma and compelling histories of asthmatic responses following wine consumption, as ascertained by structured telephone interviews, were screened for participation in the study, which was approved by the Human Research Ethics Committee at Sir Charles Gairdner Hospital. All patients reported multiple episodes of worsening asthma symptoms within 1 h of consuming either white or red wine, or both. Patients were defined as having stable asthma if (i) they had not awakened at night due to asthma on more than four occasions in the previous month, (ii) they had not required

short-acting bronchodilator medication more than twice per day (on average) in the previous month, (iii) they had not been admitted to hospital due to an asthma exacerbation in the previous 2 months and (iv) they had not received oral corticosteroid treatment in the previous 2 months.

Patients with liver disease or other serious medical conditions or who were taking medications known to interact with alcohol, or whose history suggested significant illness following consumption of wine or alcohol, were excluded. Skin prick testing was performed with five common aeroallergens. All patients had their baseline spirometry assessed during initial screening and were required to have an FEV₁ >1.0 L and >70% of predicted to be eligible to participate in the study. Of the 13 patients screened, two did not satisfy the minimum lung function criteria for recruitment into the study.

Study design

This was a double-blind, randomized study with patients consuming either high- or low-sulphite wine on separate study days. Patients were asked to abstain from alcoholic drinks for 24 h before each study day and were instructed to consume a light meal 1 h before baseline testing. Inhaled corticosteroids and short-acting β_2 -agonists were withheld for 8 h, and long-acting β_2 -agonists and anti-histamines for 48 h before wine challenge. On each study day, baseline lung function was assessed, and pre-challenge BHR to histamine was measured. After a 30-min recovery period, and if the FEV₁ was within 10% of the baseline value, the patient was asked to consume 150 mL of wine over a 5-min period. For each patient, the choice of either white or red wine was based on the patient's history of wine sensitivity, with the type of wine causing most problems being used for challenges. Spirometry was performed immediately after, and at 15 and 30 min after wine consumption. If the FEV₁ at 30 min was within 10% of the baseline value, post-challenge BHR was assessed. The study design is represented diagrammatically in Fig. 1. On a second study day at least 48 h after the first, and if the baseline FEV₁ was within 10% of the value on the first study day, an identical challenge was performed using the alternate wine. In patient 5, a significant change in BHR was observed after consumption of both high- and

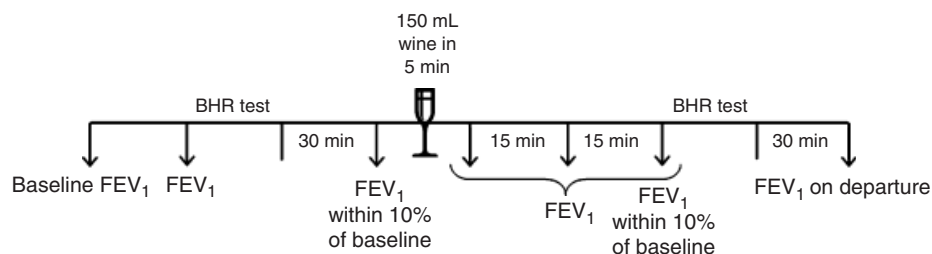


Fig. 1. Study design. FEV₁, forced expiratory volume in 1 s; BHR, bronchial hyperresponsiveness.

low-sulphite wines, and consequently on a third study day the patient consumed a placebo wine drink in a single-blind challenge.

Two patients were withdrawn from the study because their FEV₁ values did not return to within 10% of the baseline, 30 min after pre-challenge BHR testing, and one patient was withdrawn because of an unacceptably large decrease in FEV₁ (36%) on inhalation of the lowest dose of histamine during pre-challenge BHR testing. Therefore, eight patients completed the challenges with both high- and low-sulphite wines, with one patient also being challenged with placebo wine. The demographic details, asthma characteristics and wine sensitivities of these eight patients are presented in Table 1.

Challenge drink preparation

Commercially available low-sulphite white and red wines (BRL Hardy Wine Co., Reynella, SA, Australia) containing <20 p.p.m. of sulphite were used for the low-sulphite wine challenges. High-sulphite wine was prepared by adding sodium metabisulphite to the low-sulphite wines, to bring the final sulphite concentration to 250–300 p.p.m. [6]. A placebo white wine drink based on the model wine of Halpern *et al.* [4], as modified by Vally *et al.* [6], was also prepared for one patient in the study. This drink contained vodka, water, sucrose and tartaric acid with yellow curcumin dye. The pH (~3.5) and alcohol content were matched with those of the white wine used in this study. All challenge drinks were stored and consumed at room temperature.

Bronchial hyperresponsiveness testing

BHR was measured using the standard method described by Cockcroft *et al.* [15]. After measurement of baseline FEV₁, subjects inhaled a control 0.9% saline solution for 2 min, followed by doubling concentrations of histamine (0.06–8.0 mg/mL) for 2 min at 5-min intervals. FEV₁ was

measured at 30, 90 and 120 s after the end of each inhalation. The procedure was continued until a decrease in FEV₁ of at least 20% from baseline was recorded, or the maximum dose of histamine was reached.

Data analysis

BHR was measured as the concentration of histamine leading to a 20% decrease in FEV₁ (PC₂₀). A difference of greater than one doubling dose of histamine between pre- and post-challenge BHR measurements was considered to be indicative of a clinically significant response in an individual subject [12, 16]. Geometric means for PC₂₀ values, with 95% confidence intervals, were calculated and the differences between mean values were assessed for statistical significance by a paired *t*-test after log transformation of the data.

Results

Baseline bronchial reactivity to histamine in the eight subjects before high-sulphite wine challenge (geometric mean 2.09 mg/mL) was not significantly different from that before low-sulphite wine challenge (2.45 mg/mL). FEV₁ did not change by more than 15% in any of the subjects, following challenge with either high- or low-sulphite wine (Table 2). However, clinically significant or borderline significant changes in BHR were observed in four of the eight subjects. Patient 5 demonstrated clinically significant increases in BHR following challenge with both high- and low-sulphite wines. This patient subsequently underwent a single-blind challenge with a placebo wine drink to which he demonstrated a smaller, but still clinically significant, increase in BHR. Patient 6 demonstrated a significant increase in BHR following challenge with low-sulphite red wine. In contrast, patient 4 showed a significant decrease in BHR when challenged with the same wine. Finally, patient 2 showed a borderline increase in BHR after both high- and low-sulphite wine challenges.

Table 1. Patient characteristics

Patient	Gender	Age (years)	Atopic	Asthma medications	Wine sensitivity	Baseline FEV ₁ (L)	Baseline FEV ₁ (% predicted)
1	F	42	Yes	ba, bc	White	2.60	109.5
2	F	38	Yes	ba, bu	White	2.03	82.5
3	F	53	Yes	ba, bu, sm celebrex	White and red	2.36	103.5
4	M	32	Yes	ba, fl	Red	3.55	92.2
5	M	51	Yes	ba, bu	White	2.78	86.0
6	F	26	Yes	ba, fl	Red and white	3.73	117
7	F	56	Yes	ba	White	1.97	97.5
8	F	31	No	ba, bc	Red	2.70	100.4

Baseline FEV₁ and percent predicted FEV₁ are the mean values for the 2 study days.

ba, β_2 -adrenoceptor agonists; bc, beclomethasone; bu, budesonide; fl, fluticasone; sm, salmeterol; FEV₁, forced expiratory volume in 1 s; F, female; M, male.

Table 2. Changes in FEV₁ and BHR following wine consumption

Patient (wine type)	High-sulphite wine				Low-sulphite wine			
	FEV ₁ (L)		PC ₂₀ histamine (mg/mL)		FEV ₁ (L)		PC ₂₀ histamine (mg/mL)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1 (white)	2.45	2.64	5.74	8.0	2.31	2.56	4.35	6.96
2 (white)	2.10	2.10	<i>0.20</i>	<i>0.10</i>	2.12	2.01	<i>0.25</i>	<i>0.125</i>
3 (white)	2.12	2.22	1.08	1.58	2.08	2.22	1.10	0.99
4 (red)	3.36	3.53	8.0	6.12	3.41	3.56	<i>2.67</i>	<i>8.0</i>
5* (white)	2.71	2.78	<i>2.0</i>	<i>0.34</i>	2.49	2.61	<i>3.20</i>	<i>0.43</i>
6 (red)	3.41	3.70	1.08	1.14	3.72	3.83	<i>3.91</i>	<i>0.67</i>
7 (white)	1.83	1.88	2.11	1.35	1.93	1.92	4.0	2.70
8 (red)	2.75	2.85	8.0	8.0	2.70	2.82	8.0	8.0
5* (placebo)	2.46	2.64	2.5	<i>1.16</i>				

*Patient 5 was also challenged with placebo wine drink.

Changes in PC₂₀ of ≥ 1 doubling dose of histamine are indicated in italic.

BHR, bronchial hyperresponsiveness; FEV₁, forced expiratory volume in 1 s.

Discussion

This study was carefully designed to assess whether changes in BHR would occur, following challenge of wine-sensitive asthmatic patients, and also to obtain evidence for the involvement of sulphite additives in wine-induced asthmatic responses. While the patients recruited all provided compelling histories of sensitivity to white or red wine, or both, previous studies have demonstrated that the challenge of such patients under controlled conditions results in relatively few positive responses as assessed by a clinically significant decline in FEV₁ ($>15\%$ from pre-challenge values) [6, 9]. This was confirmed in the present study in which none of the eight subjects demonstrated an appreciable reduction in FEV₁ following challenge with either high- or low-sulphite wines. In contrast, clinically significant changes in BHR were observed in three patients, with another patient exhibiting borderline significant increases in BHR. The fact that there were changes in BHR without reductions in FEV₁ is important, and suggests that the reactions occurring in the lungs of some asthmatic patients following wine consumption may not necessarily lead to a reduction in FEV₁.

Increases in BHR have previously been detected in studies assessing the sensitivity of asthmatic patients to cola drinks [12], tartrazine [13], ice [17] and a variety of foods and food chemicals [14, 18, 19]. However, the proportions of subjects demonstrating significant increases in BHR varied greatly and increases in BHR have also occurred following placebo challenges [19, 20]. This has led to the suggestion that changes in BHR are less reliable than a reduction in FEV₁ for detecting intolerance to food or food chemicals [19, 20]. The results from this study demonstrate that in some patients, wine consumption may be accompanied by changes in BHR without a reduction in FEV₁. However, there was no apparent pattern in the

observed changes in BHR and some positive responses were counterintuitive, suggesting that they may not have been solely related to wine consumption, but may have been influenced by other factors such as the marked differences in baseline BHR measured on the two challenge days for some patients. It is unclear whether these differences were real and reflect exposure to other triggers on the day of challenge, or whether such a variation resulted from the imprecision inherent in the measurement of BHR. Nevertheless, these factors may have contributed to the positive responses to wine challenge, as identified by clinically significant changes in BHR, and these positive responses therefore need to be interpreted with caution.

The decrease in BHR in patient 4 after low-sulphite red wine challenge cannot be readily explained. While consumption of alcohol *per se* has been associated with a reduction in non-specific BHR in some patients [7, 21], the absence of a similar effect following high-sulphite wine suggests that the effect was unlikely to be due to alcohol alone in this patient. In contrast, in patient 5, the increases in BHR after both high- and low-sulphite wines, and also after a placebo alcoholic drink, do suggest the possibility of a reaction to alcohol *per se*, although the increase in BHR was much less following placebo. In patient 6, the increase in BHR after challenge with low-sulphite but not high-sulphite wine may have been an anomalous observation resulting from the patient's significantly lower baseline BHR on the day the positive response was recorded. Similarly, interpretation of the borderline significant increases in BHR after both high- and low-sulphite wines in patient 2 is confounded by high-baseline BHR, as well as the imprecision inherent in measuring reactivity to low concentrations of histamine.

A doubling dose increase in histamine reactivity has previously been regarded as being clinically significant [12, 16, 19], although this is somewhat arbitrary and the reproducibility of BHR testing is probably no better than

one doubling dose under ideal conditions [22, 23]. Some investigators have also reported tachyphylaxis in asthmatic subjects following repeated histamine challenges [24, 25], but these findings were not supported by other studies [26, 27]. Therefore, the decision to measure BHR before and 60 min after wine challenge was based on previous studies [9, 12], as well as the reportedly rapid (<1 h) onset of asthmatic responses to wine [1]. While repeat BHR testing within this time frame is unlikely to have been influenced by tachyphylaxis to histamine, there are other caveats associated with BHR testing, such as sensitivity, reproducibility and the influence of baseline lung function [23], which, taken together with the findings from this study, indicate that measurement of BHR will not be generally useful for detecting reactivity to wine in asthmatic subjects.

In conclusion, this study has demonstrated that changes in BHR may occur following wine consumption in some wine-sensitive asthmatic patients, in the absence of reductions in FEV₁. However, the lack of an obvious pattern in these changes in BHR suggests that some of the positive responses were not solely related to wine consumption, but resulted from complex interactions among multiple factors that may have been peculiar to individual subjects. As a consequence, the findings did not support a major role for the sulphite additives in wine-induced asthmatic responses, but did strengthen the hypothesis that wine-sensitive asthma is likely to have a complex aetiology that may vary in individual subjects.

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References

- Vally H, de Klerk N, Thompson PJ. Alcoholic drinks: important triggers for asthma. *J Allergy Clin Immunol* 2000; **105**:462–7.
- Vally H. The prevalence, characteristics and mechanisms of alcoholic drink induced asthmatic responses. PhD thesis. The University of Western Australia, Perth, 2000.
- Vally H, Thompson PJ. Allergic and asthmatic reactions to alcoholic drinks. *Addict Biol* 2003; **8**:3–11.
- Halpern GM, Gershwin E, Ough C, Fletcher MP, Nagy SM Jr. The effect of white wine upon pulmonary function of asthmatic subjects. *Ann Allergy* 1985; **55**:686–90.
- Dahl R, Henriksen J, Harving H. Red wine asthma: a controlled challenge study. *J Allergy Clin Immunol* 1986; **78**:1126–9.
- Vally H, Carr A, El-Saleh J, Thompson P. Wine-induced asthma: a placebo controlled assessment of its pathogenesis. *J Allergy Clin Immunol* 1999; **103**:41–6.
- Vally H, Thompson PJ. Alcoholic drinks and asthma. *Clin Exp Allergy* 2002; **32**:186–91.
- Garcia-Robaina JC, de la Torre-Morin F, Sanchez-Machin I, Sanchez-Monge R, Barber D, Lombardero M. Anaphylaxis induced by exercise and wine. *Allergy* 2001; **56**:357–8.
- Vally H, Thompson PJ. Role of sulfite additives in wine induced asthma: single dose and cumulative dose studies. *Thorax* 2001; **56**:763–9.
- Pastorello EA, Farioli L, Pravettoni V *et al*. Identification of grape and wine allergens as an endochitinase 4, a lipid transfer protein, and a thaumatin. *J Allergy Clin Immunol* 2003; **111**:350–9.
- Borghesan F, Basso D, Chieco Bianchi F, Favero E, Plebani M. Allergy to wine. *Allergy* 2004; **59**:1135–6.
- Wilson N, Vickers H, Taylor G, Silverman M. Objective test for food sensitivity in asthmatic children: increased bronchial reactivity after cola drinks. *BMJ (Clin Res Ed)* 1982; **284**:1226–8.
- Hariparsad D, Wilson N, Dixon C, Silverman M. Oral tartrazine challenge in childhood asthma: effect on bronchial reactivity. *Clin Allergy* 1984; **14**:81–5.
- James JM, Eigenmann PA, Eggleston PA, Sampson HA. Airway reactivity changes in asthmatic patients undergoing blinded food challenges. *Am J Respir Crit Care Med* 1996; **153**:597–603.
- Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; **7**:235–43.
- Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977; **7**:503–13.
- Wilson NM, Dixon C, Silverman M. Increased bronchial responsiveness caused by ingestion of ice. *Eur J Respir Dis* 1985; **66**:25–30.
- James JM. Respiratory manifestations of food allergy. *Pediatrics* 2003; **111**:1625–30.
- Hodge L, Yan KY, Loblay RL. Assessment of food chemical intolerance in adult asthmatic subjects. *Thorax* 1996; **51**:805–9.
- Zwetchkenbaum JF, Skufca R, Nelson HS. An examination of food hypersensitivity as a cause of increased bronchial responsiveness to inhaled methacholine. *J Allergy Clin Immunol* 1991; **88**:360–4.
- Myou S, Fujimura M, Nishi K *et al*. Effect of ethanol on airway caliber and nonspecific bronchial responsiveness in patients with alcohol-induced asthma. *Allergy* 1996; **51**:52–5.
- Juniper EF, Frith PA, Dunnet C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978; **33**:705–10.
- James A, Ryan G. Testing airway responsiveness using inhaled methacholine or histamine. *Respirology* 1997; **2**:97–105.
- Manning PJ, Jones GL, O'Byrne PM. Tachyphylaxis to inhaled histamine in asthmatic subjects. *J Appl Physiol* 1987; **63**:1572–7.
- Connolly MJ, Stenton SC, Avery AJ, Walters EH, Hendrick DJ. Refractory period following bronchoconstriction provoked by histamine in asthmatic subjects. *Thorax* 1989; **44**:146–50.
- Ruffin RE, Alpers JH, Crockett AJ, Hamilton R. Repeated histamine inhalation tests in asthmatic patients. *J Allergy Clin Immunol* 1981; **67**:285–9.
- Polosa R, Finnerty JP, Holgate ST. Tachyphylaxis to inhaled histamine in asthma: its significance and relationship to basal airway responsiveness. *J Allergy Clin Immunol* 1990; **86**:265–71.